CON: Anesthetic Choice Makes no Difference in Delirium in Cardiac Surgery

Hilary P. Grocott, MD, FRCPC, FASE
Professor, Departments of Anesthesia & Perioperative Medicine and Surgery
University of Manitoba
Winnipeg, Manitoba, Canada

A spectrum of adverse neurologic outcomes manifest in the early postoperative period in patients having undergone cardiac surgery. Though stroke can present as a dramatic neurologic catastrophe, it thankfully remains an uncommon, though highly relevant, event with an incidence generally under 5%. (1) Other more subtle adverse outcomes, such as postoperative cognitive dysfunction (POCD) have received considerable attention. (2,3) Somewhere between stroke and POCD, lie other encephalopathic states, with delirium being most notable. Delirium is one of the most common acute neurologic consequences of cardiac surgery but has a widely variable incidence. This variability (reported from 5-80%), is in part due to differences in patient risk factors, but is also due to differences in the diagnostic criteria used to define it. (4-8) When it does occur, it has been associated with significant major morbidity as well as mortality. (9,10) Coupled with this, delirium results in a substantive increase in the utilization of healthcare resources. (11) As a result, post-cardiac surgery delirium is a common problem of major significance impacting quality of recovery, morbidity and mortality, as well as healthcare costs. (9,11,12)

Best characterized as a neurobehavioral syndrome resulting from an ill-defined but fluctuating disruption of normal neural activity, delirium is further defined by its acute onset, altered level of consciousness, and inattention. (13) The contemporary diagnosis of post-cardiac surgery delirium relies on either objective measures such as the confusion assessment method – intensive care unit (CAM-ICU) (11,14), or on ill-defined and arguably non-specific postoperative encephalopathy (with or without the need for treatment), which likely underestimates the incidence considerably. (15) Formal use of the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) criteria have been used (16), but the utility of readily available bedside screening tools, such as CAM-ICU, have substantially enhanced our ability to focus efforts on this distressing clinical entity.

The etiology and pathophysiology of delirium is incompletely defined but is undoubtedly both complex and multifactorial. (17) A number of potential contributing pathophysiologic mechanisms may precipitate and cause delirium, including cerebral ischemia (18), physiologic stress (19), altered neurotransmitter (notably the acetylcholine balance with dopamine) levels (20-22), inflammatory cytokines (23), and other interneural signal transduction abnormalities. (24,25) The complexity (and associated uncertainty) of its pathophysiology has made identification of therapeutic options difficult. Though many studies have attempted to reduce the incidence and severity using both pharmacologic and non-pharmacologic approaches (26), few have had any meaningful success.

Despite its enormous significance, unfortunately few, if any, preventative or therapeutic strategies are available to meaningfully address it. The choice of anesthetic agent is no different and there is little convincing data to suggest it can make a difference. The premise that anesthetic agents can have an impact on the incidence of delirium after cardiac surgery is predicated on an assumption that events occurring intraoperatively can have direct bearing on the
subsequent development of delirium. However, the pathophysiology of delirium is sufficiently complex that it is overly simplistic to think that a single anesthetic drug (or avoidance of any on drug), administered in the intraoperative setting could have a lasting effect for the duration of the patient’s postoperative course. With the etiology of delirium being multifactorial, no single drug or nondrug therapy is likely to be sufficiently robust to prevent this troublesome illness. This does not mean that studies should not be targeted to address this issue; rather, one must be realistic in their expectations of what these trials might offer.

There are some studies, mostly observational in nature, that have attempted to address this issue. If there were to be a drug that had an impact, either positive, but more likely negative, it is likely that it would be one of the fixed agents such as benzodiazepines or opiates that we co-administer that might be contributing. It is unlikely that any volatile anesthetic by itself, despite the mixed data regarding their potential neuroprotective effect (27), or their paradoxical neurotoxic effect (28), play a role. These agents, as quickly as they reach therapeutic levels in the brain, are rapidly washed and likely have little residual effect. However, because cardiac surgery is largely being performed in the increasingly elderly patient, and the pharmacokinetics of various drugs are somewhat unpredictable in this population, it is likely that some of the fixed agents, such as benzodiazepines, may have a prolonged effect within the brain. That said, there have not been any randomized trials to investigate the long lasting cerebral effect of benzodiazepines following cardiac surgery. Interestingly, one could make a cogent argument for the fact that the administration of benzodiazepines may be the cause of delirium, (29) or that the failure to administer benzodiazepines in the chronically benzodiazepine-dependent patient might lead to disorganized brain chemistry with subsequent development of overt delirium. (30)

Other anesthetic agents that may have an impact include the use ketamine. Although again, one could easily make an argument that this N-methyl-D aspartate (NMDA) agonist might have some adverse effects on the brain (as it has been shown to be associated with hallucinogenic properties and is neurotoxic in animal models (31,32)), there is also some evidence that it may actually lead to a reduction in delirium. Indeed, Hudetz et al have performed a small, randomized pilot trial (n=58) demonstrating that a single induction i.v. dose of ketamine (0.5 mg/kg) was associated with a reduction in postoperative delirium. (33) However, until this maneuver is investigated in a much larger trial, can one ever confidently say that this may have some benefit?

Few investigations directed toward specifically investigating individual anesthetic agents (such as sevoflurane or other fixed agents such as propofol) have been undertaken with respect to their impact on incidence of delirium. What little data exists is quite contentious. Nishikawa et al (34) conducted a small study (n=50) in non-cardiac surgery patients. In this study, they examined the incidence of delirium on the first three postoperative days, as well as looking at the delirium ration score (DRS) as an indicator of delirium severity. Although the incidence of delirium in this group was no different in those managed with propofol versus sevoflurane, the DRS was significantly higher (i.e. worse) in those patients receiving propofol on postoperative days 2 to 3. However, Lurati Buse et al (35) examined the incidence of delirium in those receiving sevoflurane and propofol as well. In their trial (n=385), that was primarily directed to examine myocardial endpoints, delirium was a substudy endpoint. There was no difference in the incidence of delirium, approximately 15% in both groups, although this too was in non-cardiac surgery patients. No specific studies of these agents have been undertaken in the cardiac surgery population. Of note, Bilotta et al (36) have published the study protocol for the
PINOCCHIO trial, which is designed to examine early postoperative cognitive dysfunction and delirium in a randomized controlled trial. This large trial (n>1000) is hoped to provide some additional insight in this area.

Although anesthetic agents themselves may not have a direct impact, other drugs delivered (by anesthesiologists) intraoperatively, such as phosphodiesterase inhibitors and their co-administered anticholinergic drugs used to reverse residual neuromuscular blockade, could have an impact.

Overall, pharmacologic approaches have largely focused on treatment of delirium rather than prevention. Indeed, haloperidol has been the most widely used therapy for delirium. However, although it can reduce the severity and is still considered a first line therapy, its prophylactic use has largely failed to meaningfully decrease the overall incidence. (37) Several other pharmacologic therapies, such as the atypical antipsychotic risperidone (38), have been used with variable success. Recently, considerable study has focused on the alpha-2 adrenergic agonist dexmedetomidine. Dexmedetomidine is thought to be unique in its ability to help maintain “restful” sleep in the ICU. (39,40) Whether its main effect on reducing delirium is a unique pharmacologic effect, or secondary to a reduction in sleep deprivation is not known. The unilateral pharmacologic approach that is directed at delirium’s multifactorial etiology likely contributes to the relative lack of success with drug therapy is general. Accordingly, it is unlikely that one magic pharmacologic bullet can address all the issues associated with its development.

Intraoperative monitoring of the brain might have a role in detecting or mitigating delirium. Processed electroencephalography (EEG) such as the bispectral index (BIS) and near infrared spectroscopy (NIRS) cerebral oximetry have been examined with some interesting and compelling results. Recently, Schoen et al have identified that those patients with a low baseline cerebral saturations are at much higher risk of developing delirium following cardiac surgery. (41,42) Whether this indicates that cerebral desaturation (indicative of cerebral ischemia) is at the root cause of delirium remains unknown. There have been no interventional studies using NIRS-guided strategies to reduce delirium.

Importantly, although specific anesthetic agents have yet to be directly implicated, overall depth of anesthesia has. The use of BIS may have some ability to discriminate between those with or without risk of delirium. Most recently, Chan et al (n=921) have reported a relationship between low BIS and delirium in a trial of elderly patients undergoing major non-cardiac surgery randomized to either standard of care or a BIS guided anesthetic (with a target of 40-60). The BIS guided group demonstrated a significant reduction in delirium (15.6% vs. 24.1%, P=0.01). (43) Cerebral monitoring continues to be a promising direction for future research.

In summary, delirium after cardiac surgery is a common multifactorial problem with numerous risk factors identified. It is a highly significant postoperative problem that impairs quality of recovery, increases morbidity and mortality, and is associated with a significant increase in healthcare utilization. Although no therapies have definitively demonstrated a reduction in this complication, significant advancements have been made as the problem is being redefined and appropriately targeted with both pharmacologic and nonpharmacologic therapies. However, until the pathophysiology of delirium is better delineated, it is unlikely that the choice of anesthetic, be it a sole agent or a combinations of volatile and fixed agents, are going to have any effect.
References


