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Authors

Liu, Hong
Ji, Fuhai
Peng, Ke
et al.

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Sedation After Cardiac Surgery: Is One Drug Better Than Another?

Hong Liu, MD,* Fuhai Ji, MD,*† Ke Peng, MD,† Richard L. Applegate II, MD,* and Neal Fleming, MD, PhD*

The classic high-dose narcotic-based cardiac anesthetic has been modified to facilitate a fast-track, rapid recovery in the intensive care unit (ICU). Postoperative sedation is consequently now an essential component in recovery of the patient undergoing cardiac surgery. It must facilitate the patient's unawareness of the environment as well as reduce the discomfort and anxiety caused by surgery, intubation, mechanical ventilation, suction, and physiotherapy. Benzodiazepines seem well suited for this role, but propofol, opioids, and dexmedetomidine are among other agents commonly used for sedation in the ICU. However, what is an ideal sedative for this application? When compared with benzodiazepine-based sedation regimens, nonbenzodiazepines have been associated with shorter duration of mechanical ventilation and ICU length of stay. Current sedation guidelines recommend avoiding benzodiazepine use in the ICU. However, there are no recommendations on which alternatives should be used. In post-cardiac surgery patients, inotropes and vasoactive medications are often required because of the poor cardiac function. This makes sedation after cardiac surgery unique in comparison with the requirements for most other ICU patient populations. We reviewed the current literature to try to determine if 1 sedative regimen might be better than others; in particular, we compare outcomes of propofol and dexmedetomidine in postoperative sedation in the cardiac surgical ICU. (Anesth Analg 2017;124:1061–70)

The classic high-dose narcotic "cardiac" anesthetic became a standard of care because of the associated intraoperative hemodynamic stability and minimal depression of cardiac function. The concomitant requirement for prolonged postoperative ventilation was an acceptable tradeoff. However, as surgical and anesthetic options have evolved, it is now easier to accomplish the same intraoperative goals with management options that do not require extended postoperative mechanical ventilation. The opportunity to avoid the morbidity associated with prolonged ventilation, shorten lengths of stay in the intensive care unit (ICU) and in the hospital, and improve outcomes drove the development of "fast-track" cardiac surgery defined as the extubation of a patient undergoing open cardiac surgery within the first 6 postoperative hours.[1–3] This concept is now well accepted and widely practiced among cardiac anesthesiologists and cardiac surgery ICU physicians. To facilitate this earlier extubation, a "light" or "cooperative" sedation is required. However, the same intraoperative goals of hemodynamic stability and the absence of cardiac depression that drove the development of the high-dose narcotic cardiac anesthetic are still required in postcardiac surgery patients who still often require infusions of inotropes and vasoactive medications so that the search for the ideal sedative for this clinical application continues.

What is the ideal sedative for this patient population? An ideal drug would keep the patient comfortable without anxiety or recall of care requirements that can be unpleasant. It would effectively provide adequate sedation, but also allow neurologic evaluation of the patient, ideally without stopping administration of the drug. It would have minimal hemodynamic and respiratory depressant effects. It also would have a rapid onset and offset of action without drug accumulation or active metabolites, making it easily titratable and allowing rapid recovery with a prompt return to normal activity after discontinuation even in patients with compromised hepatic or renal function. It would not be associated with any additional adverse outcomes such as respiratory depression, major adverse cardiocerebral events, and end-organ injuries (Table 1). Is such a magic drug available? Right now, no, not yet.

Early studies of fast-track recovery reported that benzodiazepines and propofol were the most commonly used sedatives for this application.[4] More recently, studies have suggested that sedation with nonbenzodiazepine agents is associated with less mechanical ventilation time and shorter ICU length of stay (LOS). Consequently, current guidelines recommend lighter levels of sedation to manage ventilated patients preferably using nonbenzodiazepine sedatives (Recommendation: Class IIb).[5–12] However, there is currently no consistent recommendation regarding which nonbenzodiazepine sedative agents should be used. It has been suggested that both propofol and dexmedetomidine are able to provide adequate sedation for this application (Table 2).[13,14] In keeping with this suggestion, dexmedetomidine together with propofol has come to be the most widely used sedative hypnotic agents in the cardiac ICU.[14,15] This review focuses on the use of propofol and dexmedetomidine as adjuncts

From the *Department of Anesthesiology and Pain Medicine, University of California Davis Health System, Sacramento, California; and †Department of Anesthesiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu/China.

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Address correspondence to Hong Liu, MD, Anesthesiology and Pain Medicine, University of California Davis Health System, 4150 V St, Suite 1200, Sacramento, CA 95817. Address e-mail to hualiu@ucdavis.edu.

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to fast track the recovery of patients undergoing cardiac surgery, comparing and contrasting their advantages and disadvantages in postcardiac surgery patients in the ICU.

PROPOFOL

Propofol is a short-acting, intravenous (IV) hypnotic/anesthetic agent. Currently, it is the most commonly used continuous infusion sedative in the ICU.[4] Its mechanisms of action are through potentiation of the central inhibitory neurotransmitter γ-aminobutyric acid receptor activity and also through sodium channel blockade (Figure 1). Its clinical uses include induction and maintenance of general anesthesia, sedation for mechanical ventilation, and procedural sedation.

Propofol is a general central nervous system depressant. It is not selectively amnestic or analgesic but is an effective sedative largely because of its pharmacokinetic profile. Propofol is highly protein-bound and is rapidly metabolized (conjugated) in the liver. It has a short redistribution half-life (2–3 minutes), a β-elimination half-life of 30 to 60 minutes, and a terminal elimination half-life of 5 to 10 hours. A longer terminal elimination half-life (50 ± 18 hours) is expected in patients requiring prolonged sedation. The favorable kinetics facilitate dose adjustments is essential for facilitating neurologic examinations shortly after its discontinuation.[14,16]

Propofol has also been widely studied with respect to its ability to provide myocardial protection in the hope that this would extrapolate to a beneficial effect in the cardiac surgery patient population. In preclinical studies, it has been shown to provide protection against cardiac insults in a variety of experimental models.[17–20] The proposed mechanisms for these observations include upregulating the nitric oxide synthase system, acting as a free radical scavenger to enhance tissue antioxidant capacity, inhibiting calcium channels,[21–25] inhibiting mitochondrial permeability transition pore opening,[19] and providing antiapoptotic effects.[26] It has been shown to be cardioprotective when added as a supplement to cardioplegia in patients undergoing coronary artery bypass graft (CABG) or aortic valve replacement surgery.[27] Early clinical studies reported no change in coronary sinus flow, myocardial oxygen consumption, or myocardial lactate extraction after administration. By avoiding bolus injections, most investigators have shown that propofol use in cardiac surgery is not associated with the hypotension usually observed after bolus doses used for rapid induction of anesthesia.[28] It has also been reported that ICU patients who received propofol sedation had a lower acute kidney injury (AKI) rate than those who received midazolam sedation.[29] Because of these favorable kinetic and dynamic properties, propofol has been used as one of the major ICU sedative agents for postcardiac surgery patients (82.2%).[4] However, when compared with volatile anesthetics, propofol is less favorable in patients undergoing cardiac surgery. Studies have demonstrated that volatile anesthetics are associated with better preserved cardiac function after cardiopulmonary bypass, less postoperative release of troponin I, less mortality along with fewer pulmonary and other complications compared with propofol.[30,31]

However, there are also several adverse effects associated with propofol that limit its utility. It does have both direct and indirect myocardial depressant effects that can induce circulatory compromise, especially in patients who have unstable vital signs or limited myocardial reserve.[32–34] It is also a respiratory depressant drug, which can delay weaning from mechanical ventilation. It may also cause propofol infusion syndrome (PIS). PIS is a rare and the incidence is <0.37%,[35] a potentially fatal syndrome that affects patients undergoing long-term treatment with high doses of propofol (>4 mg/kg/h for more than 24 hours). It presents with cardiac failure, rhabdomyolysis, metabolic acidosis, renal failure, hyperkalemia, high blood triglycerides, and liver enlargement. It occurs more commonly in children

Table 1. The Ideal Sedative Agents

Characteristics
No venous irritation on intravenous injection
Effective clinical sedation
Rapid onset of action
Rapid recovery
Titratability
Hemodynamic stability
Prompt return of mental clarity after discontinuation
Facilitates neurologic evaluation without stopping the medication
Rapid clearance
Low reliance on end-organ metabolism
No active metabolites
No associated adverse outcomes or decreased morbidity/mortality

Table 2. Comparison of Different Sedatives[6,14,64,74,91–94]

Agent	Advantages	Disadvantages
Benzodiazepines	Antiepileptic effects, alleviate anxiety, inexpensive	Prolonged weaning, respiratory depression, hypotension, delayed awakening, increased risk of delirium
Propofol	Lack of accumulation, quick onset, fast recovery, easy adjustment	Pain on injection, hypotension, respiratory depression, hypertriglyceridemia, propofol infusion syndrome
Dexmedetomidine	Arousable with verbal commands, alleviate anxiety, analgesic properties, without respiratory depression, reduced delirium, reduced mechanical ventilation, improved mortality	Bradycardia, transient hypertension, hypotension, limited FDA-approved duration of use, nausea, dry mouth, inadequate for providing deeper sedation levels
Opioids	Analgesia and cosedative	Prolonged weaning,[a] hypotension, respiratory depression, constipation, increased risk of delirium, tachycardia (morphine), bradycardia (fentanyl)
Volatile anesthetics	Easy adjustment, shorter extubation times, reduced mechanical ventilation, stable hemodynamics	Respiratory depression, increased risk of delirium, reduced mobility, hypotension

Abbreviation: FDA, US Food and Drug Administration.
[a]Excluding remifentanil.

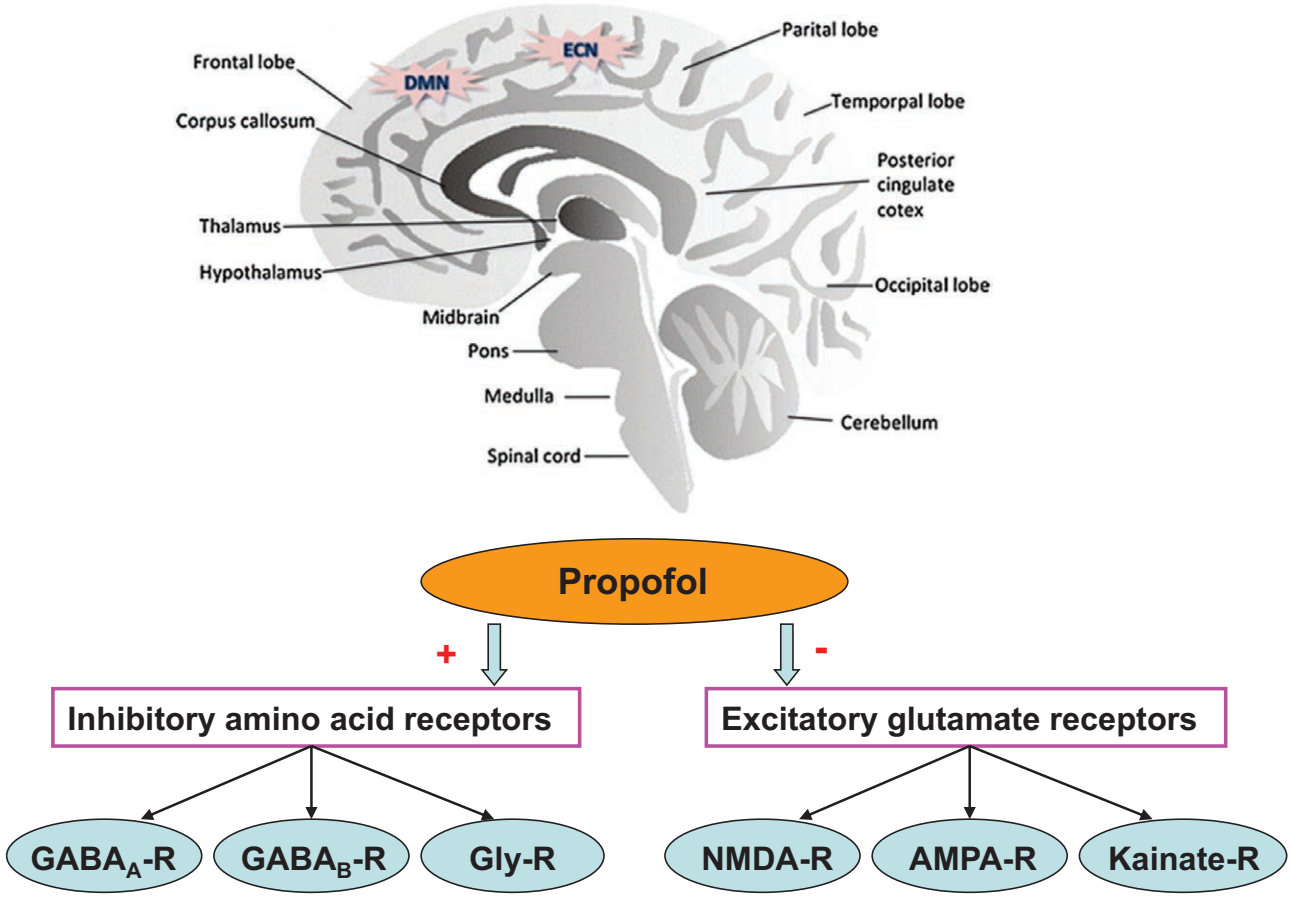

Figure 1. Brain areas associated with propofol anesthetic effects are frontal and parietal lobes (DMN and ECN), thalamus, hypothalamus, posterior cingulate cortex, and pons. GABA indicates γ-aminobutyric acid; Gly, glycine; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. (Part of the figure was adopted from Song X, Yu B. *J Anesth*. 2015;29:279–288 published by Springer with permission.)

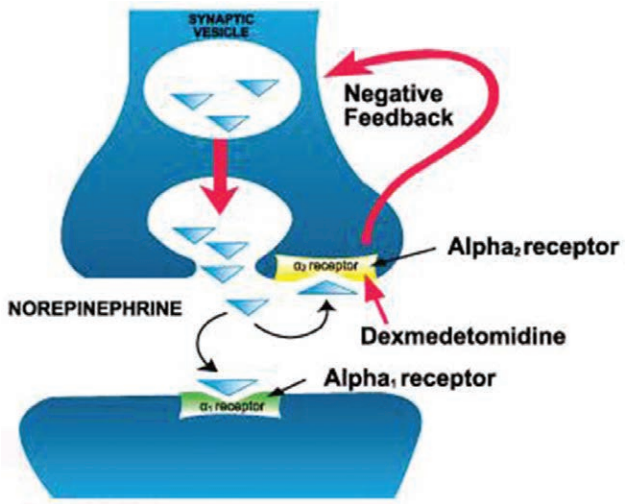

Figure 2. Mechanisms of action: dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties. The presynaptic sites of action are clinically significant because they modulate the release of norepinephrine and adenosine triphosphate through a negative feedback mechanism. (Part of the figure was adopted from Giovannitti JA Jr, Thoms SM, Crawford JJ. *Anesth Prog*. 2015;62:31–39 published by Allen Press with permission.)

and critically ill patients who receive catecholamines and glucocorticoids.[36]

DEXMEDETOMIDINE

Dexmedetomidine, an alpha-2 (α_2) adrenergic agonist, is a centrally acting sympatholytic, sedative, analgesic, and amnestic agent structurally related to clonidine. When compared with clonidine, it has a more selective α_2 agonist with an α_2:α_1 selectivity ratio of 1620:1. Dexmedetomidine acts at presynaptic, postsynaptic, and extrasynaptic receptors. Among these 3, the presynaptic sites of action are clinically more significant because they modulate the release of norepinephrine (NE) and adenosine triphosphate.[37] The α-2 agonists modulate central NE release by binding to presynaptic autoreceptors, which in turn mediates the feedback inhibition of NE release (Figure 2). Another major control mechanism for noradrenergic neurotransmission is the termination of signaling by presynaptic NE transporter-mediated NE reuptake.[38] The α-2 receptor has 3 subtypes that mediate the varied pharmacodynamics effects of dexmedetomidine. Activation of α_{2a} receptors promotes sedation, hypnosis, analgesia, sympatholysis, neuroprotection, and inhibition of insulin secretion. Stimulation at the α_{2b} receptor suppresses shivering centrally, promotes analgesia at spinal cord sites, and induces vasoconstriction in

peripheral arteries. The α_{2c} receptor is associated with the modulation of cognition, sensory processing, mood- and stimulant-induced locomotor activity, and regulation of epinephrine outflow from the adrenal medulla. Inhibition of NE release appears to be equally affected by all 3 α_2 receptor subtypes.[39] Those actions are mediated through decreases in intracellular cAMP, an efflux of potassium through calcium-activated potassium channels, and an inhibition of calcium entry through calcium channels.[40]

Dexmedetomidine has a slower onset of action with maximal effects achieved approximately 15 min after IV administration. Peak concentrations are usually achieved within 60 minutes after initiating a continuous IV infusion. It has a rapid distribution phase ($t_{1/2}$ α) of approximately 6 minutes in adults over the suggested dose ranges of 0.2 to 0.7 μg/kg/h and an elimination half-life ($t_{1/2}$ β) between 2.0 and 2.5 hours.[41] The context-sensitive half-time for dexmedetomidine is stable after prolonged infusions, but longer than that of propofol and varies more with patient age and coexisting disease. Dexmedetomidine is extensively metabolized in the liver (glucuronidation and biotransformation) by the cytochrome P450 enzyme system with no known active or toxic metabolites. However, hepatic clearance may be decreased by as much as 50% of normal with severe liver disease, and it is recommended that the dose be adjusted in patients with hepatic failure (Dexmedetomidine [package insert]; Hospira, Lake Forest, IL; September 2010). Its clearance is also dependent on cardiac output and hepatic blood flow, which potentially could increase its duration of action in patients with compromised cardiac function. Inactive metabolites are eliminated primarily in the urine (95%) and consequently may accumulate in patients with impaired renal function.[42]

The clinical applications for dexmedetomidine have evolved over recent years. It was originally evaluated as an anesthetic adjunct but ultimately marketed for use as a sedative in the ICU. Subsequent off-label use triggered a re-evaluation as an anesthetic adjunct in lower doses than initially studied. It is now widely used in both the ICU and the operating room as a sedative infusion and as an anesthetic adjunct during both general anesthesia and monitored anesthetic care. Similar to propofol, dexmedetomidine has been demonstrated to have multiple beneficial cellular effects including myocardial protection, renal protection, prevention of brain dysfunction, and enhancing anti-inflammatory effects.[43–45] In practice, dexmedetomidine provides clinically effective sedation, analgesia, anxiolysis, and inhibition of central sympathetic outflow without significant myocardial depression.[46–48] Dexmedetomidine does not cause respiratory depression. It preserves respiratory drive so that at clinically effective doses, sedation with continuous IV dexmedetomidine infusion does not delay the normal course of ventilator weaning and extubation.[48] When compared with midazolam or placebo, a dexmedetomidine infusion provides a safe, effective adjunctive analgesia. It reduces perioperative narcotic consumption, decreases the incidence of delirium, and is associated with significantly better neurocognitive function without undesirable hemodynamic effects in patients undergoing cardiac surgery.[49,50] Dexmedetomidine has been shown to mimic a nature sleep pattern and provide favorable sedative properties and minimize the use of secondary sedatives.[51]

Although dexmedetomidine has many desirable pharmacodynamic and pharmacokinetic properties, hypotension and bradycardia are the common reported complications during dexmedetomidine infusion, especially in patients with cardiovascular disease.[43] Cardiac arrest induced by dexmedetomidine has been reported.[52]

COMPARISONS BETWEEN PROPOFOL AND DEXMEDETOMIDINE FOR POSTCARDIAC SURGERY SEDATION

Adequate levels of sedation can be achieved by either dexmedetomidine or propofol in ICU patients who require mechanical ventilation.[53] Propofol or dexmedetomidine alone has shown favorable outcomes when compared with placebo for postcardiac surgery sedation. There are several studies comparing propofol and dexmedetomidine given by continuous infusion for short-term postoperative sedation in adult patients who underwent CABG and/or cardiac valve surgery (Table 3). The following words were used to conduct a basic search: cardiac surgery or heart surgery and dexmedetomidine or propofol and sedation in EMBASE, PubMed, the Cochrane Library, and Science Citation Index from 1988 to 2016. The studies were focused on the incidence of postoperative delirium (POD), duration of mechanical ventilation, time to extubation, requirements for supplemental sedatives and rescue agents, hemodynamic effects, effect on vital organ function, ICU LOS, hospital LOS, and health care costs because those parameters are most often used in the outcome studies in postcardiac surgery ICU patients.

Delirium

Delirium is an acute fluctuation in mental status that manifests with inattention, disorganized thinking, and/or an altered level of consciousness.[71] POD occurs more frequently after cardiac surgery and the incidence has been reported to be as high as 52%.[72] One study demonstrated that the duration of delirium was the strongest independent predictor of death, ventilation time, and ICU stay.[73] When compared with propofol, dexmedetomidine sedation reduces the incidence, delays the onset, and shortens the duration of POD without undesirable hemodynamic effects in postcardiac surgery patients.[49,56,74] In 1 report, the incidence of delirium for patients receiving dexmedetomidine was 3% as compared with 50% for the patients receiving propofol and midazolam.[65] Patients sedated with dexmedetomidine have been reported to have a lower risk of delirium after cardiac surgery.[69]

Duration of Mechanical Ventilation

Ventilator-associated pneumonia (VAP) is the leading cause of nosocomial morbidity and mortality. Patients undergoing cardiac surgery have a higher incidence of VAP, especially those who require longer postoperative ventilation. Earlier extubation and shorter duration of respiratory support decrease the risk for and occurrence of VAP.[75] A majority of studies have suggested that dexmedetomidine-based sedation resulted in shortened ventilation times and early

Table 3. Postoperative Sedation: Dexmedetomidine, Propofol, and Benzodiazepines

Study	Design	Patients (n)	Main Outcomes
DEX vs control			
Priye, 2015[49]	Prospective	Cardiac ICU (64)	DEX reduced pain scores and fentanyl consumption ($P < .001$) with a trend toward reduced delirium (3.1% vs 15.6%, $P = .086$)
Narisawa, 2015[54]	Retrospective	Cardiac ICU (45)	DEX reduced nighttime heart rate (69.9 ± 11.3 vs 84.3 ± 9.6, $P < .001$) and atrial fibrillation (multivariate analysis, $P = .045$)
Chorney, 2013[55]	Retrospective	Cardiac ICU (99)	More acetaminophen use was associated with DEX ($P = .02$); no difference for bradycardia, hypotension, or extubation time
DEX vs PRO			
Djaiani, 2016[56]	Prospective	Cardiac ICU (183)	DEX reduced delirium (17.5% vs 31.5%, $P = .028$), delayed onset ($P = .027$), and shortened duration of delirium ($P = .04$)
Conti, 2016[57]	Prospective	ICU (20)	DEX may offer some advantages in terms of patient–ventilator synchrony with lower asynchrony index at 12 h (2.68% vs 9.10 %, $P < .05$)
Paliwal, 2015[53]	Prospective	ICU (60)	DEX reduced heart rate with more rescue sedation (60% vs 20%, $P = .0398$) and bradycardia ($P < .01$); PROP transiently reduced MAP ($P < .01$)
Karaman, 2015[1]	Prospective	Cardiac ICU (64)	DEX reduced extubation time (265.94 ± 43.1 vs 322.52 ± 39.2 min, $P < .001$) with higher patient satisfaction (9 [7–10] vs 7[5–9], $P < .001$)
Anger, 2010[58]	Prospective	Cardiac ICU (56)	DEX resulted in a higher incidence of hypotension (61% vs 32%, $P = .04$) and analgesic consumption (25% vs 3.6%, $P = .05$)
Herr, 2003[59]	Prospective	Cardiac ICU (295)	DEX reduced the use of morphine (28% vs 69%, $P < .001$), tachycardia ($P = .007$), the use of β-blockers ($P = .014$), antiemetics ($P = .015$), epinephrine ($P = .030$), and diuretics ($P < .001$)
Thoma, 2014[60]	Retrospective	Cardiac ICU (84)	DEX reduced mechanical ventilation time (11.8 ± 22.3 vs 22.6 ± 39.9 h, $P < .01$), ICU and total LOS ($P < .05$), and medical costs ($2613 per patient)
Curtis, 2013[61]	Retrospective	Cardiac ICU (582)	DEX reduced extubation time (8.8 vs 12.8 h, $P = .026$), hospital LOS (181.9 vs 221.3 h, $P = .001$), and medical costs ($4000 per patient)
Torbic, 2013[62]	Retrospective	Cardiac ICU (126)	DEX reduced length of mechanical ventilation (5.0 [3.6–7.0] vs 9.8 [5.0–16.3], $P = .0001$) with greater hemodynamic stability and arousability
Barletta, 2009[63]	Retrospective	Cardiac ICU (100)	DEX reduced opioid requirements (0 [0–10 mg] vs 4 [0–33 mg], $P < .001$) but not affect duration of mechanical ventilation
Xia, 2013[64]	Meta-analysis	ICU (1202)	DEX reduced ICU LOS (MD = −0.81 d, $P = .017$) and delirium (RR = 0.40, $P = .003$) but not duration of mechanical ventilation or ICU mortality
PROP vs BDZ			
Leite, 2015[29]	Retrospective	ICU (1396)	PROP improved renal-related outcomes (55.0% vs 67.3%, $P < .001$) and ICU mortality (14.6% vs 29.7%, $P < .001$)
DEX vs BDZ and PROP			
Maldonado, 2009[65]	Prospective	Cardiac ICU (118)	DEX reduced delirium (3% vs 50% for BDZ, and 50% for PROP) and care costs
Klompas, 2016[13]	Retrospective	ICU (9603)	DEX reduced extubation time (HR = 2.3 vs BDZ; HR = 1.7 vs PROP) but not hospital discharge or mortality
Barr, 2013[14]	Guidelines	ICU (19,000)	Favoring the use of IV DEX or PROP over BDZ sedatives
Cruickshank, 2016[66]	Meta-analysis	ICU (2489)	DEX reduced ICU LOS (MD = −1.26 d, $P = .0004$) and time to extubation (MD = −1.85 d, $P < .00001$) but did not affect mortality
Constantin, 2016[67]	Meta-analysis	ICU (1994)	DEX reduced ICU LOS (MD = −0.304, $P = .001$), mechanical ventilation duration (MD = −0.313, $P = .003$), and delirium (RR = 0.812, $P = .020$)
Fraser, 2013[6]	Meta-analysis	ICU (1235)	DEX or PROP rather than BDZ-based sedation reduced ICU LOS (MD = −1.62 d, $P = .0007$) and mechanical ventilation (MD = −1.9 d, $P < .00001$)
Nelson, 2015[68]	Systematic review	ICU (492)	DEX may reduce delirium but the results were inconclusive
DEX vs control, BDZ, and PRO			
Li, 2015[50]	Meta-analysis	ICU (2612)	DEX reduced neurocognitive dysfunction (RD = −0.17, $P = .008$ vs control; RD = −0.16, $P = .009$ vs other comparators)
Lin, 2012[69]	Meta-analysis	Cardiac ICU (16,818)	DEX reduced length of mechanical ventilation (MD = −2.7, $P = .02$) and delirium (RR = 0.36, $P = .0004$) with higher risk of bradycardia (RR = 2.08, $P = .01$) but did not affect ICU stay, hospital stay, or mortality
Geng, 2016[70]	Meta-analysis	Cardiac ICU (1702)	DEX reduced ventricular tachycardia (RR = 0.28, $P = .0002$) and delirium (RR = 0.35, $P = .0004$) with more bradycardia (RR = 2.23, $P = .001$)

Abbreviations: BDZ, benzodiazepines; CABG, coronary artery bypass graft; DEX, dexmedetomidine; HR, hazard ratios; ICU, intensive care unit; IV, intravenous; LOS, length of stay; MAP, mean arterial pressure; MD, mean difference; PRO, propofol; RD, risk differences; RR, relative risks.

extubation more frequently than propofol-based sedation and may therefore be a preferable agent for mechanically ventilated cardiac ICU patients.[13,56,61,62,76] In a meta-analysis of 11 studies including a total of 16,818 patients, the authors confirmed that dexmedetomidine was associated with shorter lengths of mechanical ventilation after cardiac surgery.[69] Another study of fast-track cardiac anesthesia (FTCA) compared dexmedetomidine with propofol and found shorter extubation time and higher patient satisfaction scores in the dexmedetomidine-based sedation group.

When compared with the benzodiazepine and propofol groups, there were fewer ventilator-associated events in the dexmedetomidine group.[13] The lower risk oversedation, faster clearance, titrated protocol, etc, have contributed to dexmedetomidine's promotion of faster extubation times. Moreover, because dexmedetomidine does not have as extensive a side effect profile as propofol, it has been suggested that clinicians could easily prefer dexmedetomidine over propofol in FTCA.[1]

Opioid Use

Opioid use has been associated with postoperative respiratory depression and consequent delayed extubation with prolonged ICU and hospital LOS. Minimizing opioid use is a critical component of FTCA. FTCA protocols usually use short-acting hypnotic drugs, reduced doses of opioids, or use of ultrashort-acting opioids.[2] When compared with propofol in a FTCA protocol, dexmedetomidine sedation resulted in lower opioid requirements.[63] Dexmedetomidine infusion provides safe, effective adjunctive analgesia and reduces narcotic consumption without undesirable hemodynamic side effects in patients undergoing cardiac surgery.[49] Patients sedated with propofol required 4 times the mean dose of morphine while in the ICU compared with patients sedated with dexmedetomidine.[77] The overall daily dose of supplemental analgesics in the propofol group was also significantly higher than in the dexmedetomidine group.[77] Dexmedetomidine provided safe and effective sedation for post-CABG surgery patients and significantly reduced the use of analgesics.[59]

Secondary Sedative Drugs

Patients in the ICU often periodically require a secondary agent to achieve optimal sedation. Benzodiazepines and opioids are the most commonly used supplemental agents. However, their use is also associated with longer mechanical ventilation times and longer ICU LOS, and it has therefore been suggested to use nonbenzodiazepines for ICU sedation.[5–12] Dexmedetomidine provides effective sedation with less hypotension and lower vasopressor requirements when compared with a morphine-based sedation regimen, and some studies have shown less rescue drug requirements in dexmedetomidine patient groups than in those receiving propofol.[56,68,74] Another study did not confirm this difference.[78] In additional comparisons, the desired level of sedation was achieved in both groups, but patients receiving dexmedetomidine were aroused more easily with adequate sedation when compared with patients receiving propofol. However, there was an increased use of rescue sedatives in this patient group to obtain a comparable level of sedation judged by using a Ramsey Sedation Score.[53]

Hemodynamics

Maintaining stable hemodynamics is important for all ICU patients, and it is particularly vital for postcardiac surgery patients. All sedatives have adverse cardiovascular side effects.[12] Overall, bradycardia is seen more often in patients receiving dexmedetomidine, and hypotension is seen more often in patients receiving propofol.[62,77] Decrease in heart rate and blood pressure may also be accompanied by other hemodynamic changes. After a bolus injection of propofol, there was a statistically significant decrease in mean arterial pressure, but simultaneously, there was also a significant decrease in stroke volume, cardiac output, and cardiac index together with tachycardia.[62,78] It has been suggested that dexmedetomidine sedation, rather than propofol sedation, after CABG surgery is associated with greater hemodynamic stability.[62] Atrial dysrhythmias (fibrillation, flutter), with a cumulative incidence ranging from 10% to 50%, are among the most common cardiovascular problems after cardiac surgery, and dexmedetomidine use was associated with a lower incidence of atrial dysrhythmias.[79] Dexmedetomidine has also been shown to significantly reduce the postoperative use of β-blockers, epinephrine, and diuretics.[59] The use of dexmedetomidine in treating perioperative tachyarrhythmias has been reported. However, there is also a report of cardiac arrest when dexmedetomidine was coadministered with amiodarone in a hemodialysis patient.[80] Table 4 summarizes the major effects of dexmedetomidine and propofol on hemodynamics.

Acute Kidney Injury

The rate of postoperative AKI can be as high as 30% in patients undergoing cardiac surgery. AKI is associated with

Table 4. Effects of Dexmedetomidine and Propofol on Hemodynamics

Hemodynamics	Dexmedetomidine	Propofol
HR	Reduced[a]	Not affected[81]
	Reduced	Reduced[82]
Bradycardia	17.8%	14.3%[58]
	7.4%	6.3%[83]
BP	Dose-dependently reduced, more than propofol[a]	Dose-dependently reduced[83]
Hypotension	61%, more than propofol[a]	32%[58]
	24%	31%[83]
SBP	Reduced	Reduced[82]
DBP	Reduced	Reduced[82]
CVP	−7.6%	−16.6%, more than Dex[82,a]
CI	−16.4%, more than propofol[a]	−9.5%[82]
SVI	Reduced	Reduced[82]
TSVRI	Reduced	Reduced[82]

Hypotension was defined as a mean arterial blood pressure less than 60 mm Hg, and bradycardia was defined as a heart rate less than 50 beats/min.
Abbreviations: BP, blood pressure; CI, cardiac index; CVP, central venous pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SVI, stroke volume index; TSVRI, total systemic vascular resistance index.
[a]Significant difference.

mortality rates up to 60% among all patients undergoing cardiac surgery and a 25-fold increase after cardiac valve surgeries.[84] Early detection and treatment are critical.[85] Among all the routinely used sedative agents, dexmedetomidine has a special place in the cardiac surgical setting. In the early follow-up period after CABG, the patient is subjected to the negative effects of extracorporeal circulation and the associated inflammatory surge. Because AKI has an important role in postoperative morbidity and mortality, routine clinical use of dexmedetomidine after CABG could be therapeutic. Dexmedetomidine infusion for sedation after CABG under cardiopulmonary bypass has been shown to be useful in the prevention of kidney injury, especially mild AKI in patients with preoperative normal renal function and mild chronic kidney disease undergoing cardiac surgery.[84] In a recent study, the use of a dexmedetomidine infusion in pediatric patients after congenital heart surgery was associated with a decreased incidence of AKI; however, this was not associated with changes in clinical outcomes.[86] Another study did not find differences in a cohort of relatively low-risk patients undergoing elective CABG but did report an associated increase in urinary output.[87] The renal protective property can be attributed to the promotion of renal arterial vasodilatation by sympatholysis, anti-inflammatory, and cytoprotection effects from activating cell survival signal phosphatidylinositol kinase via α_2 adrenoceptors to reduce cell death and high-mobility group protein B1 release and subsequent inhibition of toll-like receptor 4 signaling, activating the cholinergic antiinflammatory pathway.[84]

ICU Length of Stay, Hospital Length of Stay, and Cost

Health care costs and their rate of increase are unsustainable in the United States with the prediction that health care costs will be 20% of the gross domestic product by 2020.[88] Patients who develop postoperative delirium have significantly longer ICU stays and longer total hospitalizations.[65] Prolonged ICU and hospital stays are responsible for a significant portion of increased health care costs, and poignantly, they are also correlated with poor outcomes. One study has demonstrated that extra LOS related to delirium was estimated to be 9000 days resulting in an annual financial cost of $17 million.[56] Postoperative administration of dexmedetomidine-based sedation regimen resulted in reduced incidence, delayed onset, and shortened duration of POD when compared with propofol-based sedation in elderly patients after cardiac surgery, which reduced the health care cost.[56] This potential improvement in patient care and decreased cost is a major driving force behind the effort that has been made to fast track postcardiac surgery patients and correspondingly decrease postoperative ICU and hospital LOS.[2] Sedation with dexmedetomidine was associated with a 48-hour reduction in ICU LOS when compared with benzodiazepines and propofol.[62,67] Studies showed ICU LOS in the dexmedetomidine group was significantly shorter (1.1 vs 2.6 days, $P = .006$) in comparison with propofol.[64,77] Some studies have found the average ICU LOS or hospital LOS was shorter with dexmedetomidine-based sedation in postcardiac surgery patients, whereas others reported no difference.[13,60–62] Total hospital charges have been shown to be less in patients receiving dexmedetomidine as compared with the propofol group.[61] The lower charges for the ICU, operating room time, ICU, hospital room, and board and respiratory services could all contribute to the lower cost.[76] In one study, the estimated net financial benefit of choosing dexmedetomidine over propofol was $2613 per patient. Higher drug costs were offset by savings in postoperative costs.[54]

CONCLUSIONS

Sedation is an increasingly important component of postoperative patient management after cardiac surgery. Benzodiazepines, opioids, inhaled volatile anesthetics, propofol, and dexmedetomidine have all been used for sedation following cardiac surgery (Table 3). Sedation practices and outcomes have changed over the years with a swing toward lighter sedation, use of analgesics before sedatives, regular sedation monitoring using a validated scoring system, bolus as opposed to infusion administration, bedside sedation algorithms, and nurse-driven protocols, which may all affect outcomes. The updated guidelines from the Society of Critical Care Medicine recommend first-line sedation with dexmedetomidine or propofol for most ICU patients.[14] In keeping with this suggestion, dexmedetomidine, together with propofol, has come to be the most widely used sedative hypnotic agents in the cardiac ICU.[14] The US Food and Drug Administration has currently approved dexmedetomidine for sedation through IV bolus and continuous infusion for up to 24 hours in intubated adults. In Europe, dexmedetomidine is approved for adults (intubated or nonintubated) in the ICU through continuous IV infusion without a restriction on the duration of administration.[15] In this review, the authors found that most current studies favor the use of dexmedetomidine for patients with fast-track protocols, especially during the early postoperative period. Dexmedetomidine modulates undesirable increased sympathetic activity, and as a sedative agent, it does not affect the time to extubation because of its minimal effects on respiratory drive. It is also associated with a decrease in the incidence of delirium in the ICU. Propofol remains as a good alternative. There are limitations in most of the current prospective studies, largely because of small numbers of patients and single-center study designs. Some studies comparing sedative drugs were unable to demonstrate differences in common outcomes such as mechanical ventilation time, incidence of delirium, opioid use, supplemental sedative drug use, or ICU LOS. This may reflect the accumulated clinical expertise with this drug in a given institution and the associated protocols and clinical experience. Studies have demonstrated that dexmedetomidine sedation is identical to stage 2 of physiological sleep, where patients can still be comfortable but awakened easily.[89] Decreased analgesic requirements have also been consistently described with dexmedetomidine. Dexmedetomidine use has been associated with a decrease in postoperative mortality and decreased incidence of postoperative complications including AKI in patients undergoing cardiac surgery.[84,90] With such desirable properties and outcomes, dexmedetomidine is a first-line drug for the fast-track anesthesia recovery and sedation management in postcardiac surgery patients. However, with the potential

for prolonged intubation (>24 hours), other considerations come into play. For propofol, there is PIS that is more likely to occur when infusion duration exceeds 24 hours. For dexmedetomidine, there is the current US Food and Drug Administration approval limited to infusion in the ICU to 24 hours. Future studies should focus on the long-term outcomes associated with using dexmedetomidine for sedation and potential molecular structure changes/modifications that may decrease the adverse effects on blood pressure and heart rate.

In cardiac surgery, when compared with total IV anesthesia, general anesthesia with volatile anesthetics was associated with major outcome benefits, including reduced mortality as well as a lower incidence of pulmonary and other complications.[31] Inhaled volatile anesthetic-based sedation used for postcardiac surgery patients has been associated with shorter duration of mechanical ventilation, shorter extubation times, and stable hemodynamics in comparison with propofol.[91–94] Inhaled volatile anesthetic sedation was also demonstrated to provide myocardial protection against reperfusion injury in the ICU.

In conclusion, although propofol is still the most commonly used sedative for postcardiac surgery patients, the emerging use of dexmedetomidine and associated studies demonstrating outcome benefits suggest that dexmedetomidine may soon become the drug of choice in this setting. That said, there is still significant room for the improvement of our overall management of these patients. More widespread application of sedation assessments may decrease the incidence of oversedation and side effects. In addition, it is not necessary to find a single drug that covers all needs. Selective administration of lower doses of short-acting opioids, benzodiazepines, or other sedative/analgesic drugs may frequently be beneficial in some patients in some settings. Each patient is unique in his or her response to any medication. One drug is not necessarily better than another, and each must be tailored to the individual patient needs and determined by the treating physician.

DISCLOSURES

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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Name: Fuhai Ji, MD.
Contribution: This author helped complete the manuscript.
Name: Ke Peng, MD.
Contribution: This author helped complete the manuscript.
Name: Richard L. Applegate II, MD.
Contribution: This author helped write the manuscript.
Name: Neal Fleming, MD, PhD.
Contribution: This author helped complete the manuscript.
This manuscript was handled by: W. Scott Beattie, PhD, MD, FRCPC.

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