

Propofol-Based Versus Dexmedetomidine-Based Sedation in Cardiac Surgery Patients

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Objectives: To evaluate the effects of propofol-based and dexmedetomidine-based sedation regimens on achieving early extubation, length of stay (LOS), intensive care length of stay (ICU-LOS), total hospital costs, and mortality rates in cardiac surgery patients.

Design: Twenty-three-month retrospective analysis.

Setting: Single center, 907 bed community teaching hospital.

Participants: Five hundred eighty-two patients ≥ 18 years of age who received propofol-based or dexmedetomidine-based sedation after cardiac valve or coronary artery bypass grafting (CABG) surgery and who did not undergo prolonged surgery (≤ 8 hours).

Intervention: Retrospective review of medical records.

Measurements and Main Results: Baseline characteristics (eg, age, sex, comorbidities) and outcomes (eg, achievement of early extubation, LOS, ICU-LOS, total hospital costs, pharmacy costs) were collected. Early extubation was achieved more frequently in the dexmedetomidine group when compared with the propofol group (68.7% v 58.1%, $p = 0.008$). The mean postoperative time to extubation and

hospital LOS were shorter in the dexmedetomidine group when compared with the propofol group (8.8 v 12.8 hours, $p = 0.026$) and (181.9 v 221.3 hours, $p = 0.001$), respectively. There was a reduced ICU-LOS in the dexmedetomidine group compared with the propofol group that did not reach statistical significance (43.9 v 52.5 hours, $p = 0.067$). Average total hospital charges for the dexmedetomidine group were approximately \$4000.00 less than the propofol group.

Conclusions: Dexmedetomidine-based sedation resulted in achievement of early extubation more frequently than propofol-based sedation. Mean postoperative time to extubation and average hospital LOS were shorter with dexmedetomidine-based sedation and met a statistical level of significance. There was no difference in ICU-LOS or in-hospital mortality between the two groups. Total hospital charges were similar, although slightly higher in the propofol group.

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MAINTENANCE OF COMFORT while minimizing pain, anxiety, and cardiac instability secondary to sympathetic discharge are primary goals of sedation in postoperative cardiac surgery patients.¹ Proper sedation and analgesia can decrease physiologic stress responses and facilitate adequate mechanical ventilation. Many sedatives and analgesics are currently used in postoperative cardiac surgery patients to achieve the aforementioned goals; however, there is no consensus as to which agents are preferred for maximum safety, efficacy, and cost-effectiveness. Two commonly used sedatives in practice include propofol and dexmedetomidine. Studies comparing the 2 drugs in postoperative cardiac surgery patients have been performed in the past; however, there have been no head-to-head trials comparing the two sedatives with a primary goal of achieving early extubation in this population.^{2,3}

Important factors in selection of a sedative include the agent's onset of action, adverse effect profile, and quick recovery of cognition after discontinuation of the drug. Propofol, which was approved by the Food and Drug Administration (FDA) in 1993 for use as a sedative for mechanically ventilated patients in the intensive care unit (ICU), is an intravenous phospholipid emulsion that has anesthetic, sedative, and hypnotic properties.⁴ Propofol has a rapid onset of action and short duration of sedation once discontinued; therefore, pharmacokinetically, it is a favorable choice for use in cardiac surgery. Infusions of propofol must be discontinued to properly assess neurologic function. Due to the vasodilatory properties of propofol, it may cause significant hypotension in certain patients, specifically those with cardiac dysfunction or hemodynamic instability.^{5,6} Propofol does not possess analgesic effects and is typically given along with an opioid agonist such as fentanyl. Respiratory depression can result from propofol alone, and this effect can be even more profound when given in combination with an opioid agonist.^{4,7} Other

adverse effects of propofol include but are not limited to hypertriglyceridemia, bradycardia, hypotension, and lactic acidosis. It is also important to note that propofol contains no preservatives and may serve as a medium for microbial growth; therefore, tubing and unused portions of propofol must be discarded 12 hours after initial spiking of the vial.⁴

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist with sedative, anxiolytic, sympatholytic, and opioid-sparing properties that gained approval for use as a sedative-analgesic in the intensive care setting by the FDA in 1999.^{8,9} Dexmedetomidine causes sedation through stimulation of alpha-2 receptors in the central nervous system, specifically the locus coeruleus.¹⁰ Dexmedetomidine is administered as a continuous intravenous infusion and, when given at appropriate doses, does not decrease respiratory function or arterial oxygen saturation.¹¹ Adverse effects associated with dexmedetomidine most commonly include hypotension and bradycardia.¹² Dexmedetomidine infusions do not have to be stopped to assess neurologic function: the patient is in a sleep-like state but is easily aroused upon stimulation.¹³ Although dexmedetomidine is a relatively new drug, its use in postoperative cardiac surgery has rapidly expanded. The rationale behind its use in postoperative cardiac patients is that the lack of effect on respiratory function, potential for decreased opioid use, and

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sympatholytic function could lead to patients having decreased times to extubation, decreased intensive care length of stay (ICU-LOS), and decreased hospital length of stay (LOS).^{11,14}

Early extubation of cardiac surgery patients has been shown to decrease ICU-LOS and hospital LOS without an increased risk of organ dysfunction or postoperative complications.¹⁵ Prolonged mechanical ventilation is associated with an increased risk of morbidity and mortality, especially from infectious complications such as ventilator associated pneumonias.¹⁶ Intensive care areas typically carry a higher overall risk of infection when compared with the general floors.¹⁷ Additional risks associated with prolonged mechanical ventilation include gastrointestinal bleeding secondary to stress ulcer formation, pulmonary barotrauma, and decreased cardiac output.^{18–20} The practice of early extubation and minimizing the time of mechanical ventilation is expanding among many practitioners and may help in reducing morbidity and mortality. Early extubation protocols may be a valuable tool in maximizing the number of eligible patients extubated early and may decrease both hospital and ICU-LOS.²¹

METHODS

The APOLLO database is a cardiac surgery database that encompasses details about cardiac surgeries and their outcomes, which is utilized at a 907-bed community teaching hospital. The database is maintained by a dedicated cardiology staff. There were over 1,000 cardiac procedures that were performed at the hospital and logged into the database during the study period from December 2008 to October 2010. The APOLLO database was the primary source of data for this study. The data gathered from APOLLO included time to extubation, hospital LOS, ICU-LOS, type and urgency of the cardiac procedure, age, gender, primary type of sedation used, and in-hospital mortality. Duration of intubation, hospital LOS, and ICU-LOS were all calculated based on specific dates and times logged in the database. Information on co-morbidities was gathered from the hospital database using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Hospital charges were obtained from the financial database at our institution.

In July 2009, Teva Pharmaceuticals USA initiated a voluntary recall of propofol due to the presence of elevated endotoxin levels in some contaminated vials. Propofol then became unavailable from Hospira Inc, in March 2010 due to potential particulate contamination.^{22,23} Prompted by the short supply and subsequent unavailability, the sedative of choice for cardiac procedures at the study institution was changed from propofol to dexmedetomidine in November 2009. Secondary to this shift in sedative use, the study was able to be designed around two specific time periods to collect a large sample of patients in both sedative groups. Inclusion criteria for this study were patients ≥ 18 years of age admitted for either coronary artery bypass grafting (CABG), valvular surgery, or CABG and valvular surgery between December 1, 2008 and October 31, 2010 who received either propofol or dexmedetomidine as their primary postoperative sedative. Patients were excluded if they spent a prolonged time in surgery (> 8 hours). These patients were excluded because they likely had complications that would not be representative of a typical cardiac surgery. A total of 978 patients met the inclusion criteria for this study (455 dexmedetomidine, 523 propofol). The required sample size to achieve a power of 80% was 291 patients per group, or 582 total (Fig 1). The calculated sample size assumed a 62.5% early extubation rate in the propofol group and a 15% improvement in the dexmedetomidine group. The assumption of an early extubation rate of 62.5% with

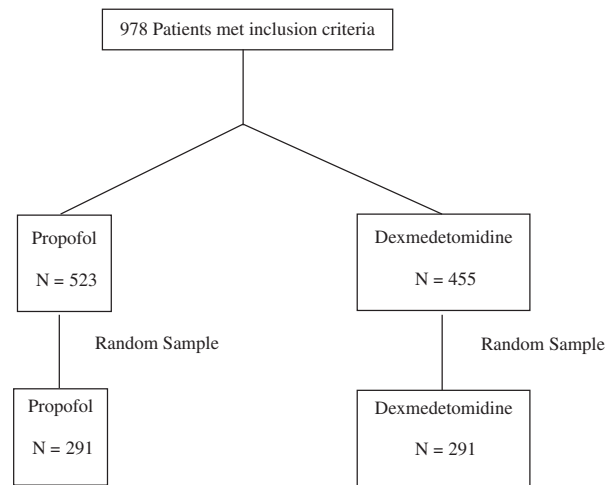


Fig 1. Enrolled patients flow diagram. This depicts the flow of all patients screened and included.

propofol-based sedation was based on data previously analyzed at this institution. The population was randomized to reduce the chance of a selection bias.

The goal of this study was to evaluate the effects of propofol-based and dexmedetomidine-based sedation in postoperative cardiac surgery patients in clinical practice. The primary objective measured by this study was the achievement of early extubation, defined as postoperative extubation of ≤ 6 hours. The study center's cardiac surgery program has a goal time to extubation of ≤ 6 hours for postoperative cardiac surgery patients. Secondary objectives included hospital LOS, ICU-LOS, in-hospital mortality, and total hospital charges. Baseline characteristics including, age, gender, co-morbidities, the type of cardiac procedure performed, the urgency of the procedure, and charges were reported. Elective surgery is defined as stable cardiac function in the days or weeks before the operation and the option to defer the procedure without increased risk of compromised cardiac outcome. Urgent surgery is defined as surgery that is required during the same hospitalization to minimize chance of further clinical deterioration. Emergent surgery is defined as patients having ongoing and refractory cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except cardiac surgery.²⁴ During the study period, the sedation protocol as well as weaning assessment protocol remained unchanged. Patients were assessed on an ongoing basis postoperatively for readiness to wean. If the patient met predefined criteria, extubation was performed. All analyses were conducted by using SPS software. Statistics for nominal data (early extubation and in-hospital mortality) were conducted using Pearson's chi-square procedure. Statistics for continuous data (hospital LOS, ICU-LOS, time to extubation, costs) were conducted through the Student's *t* test. All tests were conducted at an alpha level of 0.05.

RESULTS

A total of 582 patients were included in this study. No significant differences in demographics were observed between treatment groups (Table 1). Patients in the dexmedetomidine group were slightly older than those in the propofol group (67.6 v 65.7 years), and both groups consisted of predominantly males (200 in the dexmedetomidine group and 190 in the propofol group). The dexmedetomidine group had fewer patients with obesity (BMI ≥ 30) (114 v 135) and congestive heart failure (45 v 60) than those in the propofol group.

Table 1. Baseline Demographic Characteristics

Characteristic	Dexmedetomidine (n = 291)	Propofol (n = 291)	p value
Age (years)	67.6	65.7	0.065
Gender (female)	91 (31.3%)	101 (34.7%)	0.378
Ethnicity	–	–	0.611
Hispanic	5 (1.7%)	7 (2.4%)	–
Caucasian	258 (88.7%)	253 (86.9%)	–
African-American	26 (8.9%)	25 (8.6%)	–
Other	2 (0.7%)	6 (2.0%)	–

Hypertension (191 v 186), obstructive sleep apnea (OSA) (20 v 18), and chronic obstructive pulmonary disease (COPD) (58 v 55) occurred more frequently in the dexmedetomidine group than in the propofol group. Co-morbidities between the two groups were similar with no statistically significant differences found (Table 2).

In the dexmedetomidine group, 179 (61.5%), 76 (26.1%), and 36 (14.4%) patients underwent CABG, valve surgery, or CABG and valve surgery, respectively. Similarly, in the propofol group, 186 (63.9%) patients underwent CABG, 63 (21.6%) valve surgery, 42 (14.4%) had CABG and valve surgery. In the dexmedetomidine group, 154 (52.9%) cases were elective, 132 (45.4%) were urgent, and 5 (1.7%) were emergent. The propofol group resulted with 108 (37.1%), 176 (60.5%), and 7 (2.4%) elective, urgent, and emergent cases (Table 3).

Early extubation, the primary objective, was achieved more often in the dexmedetomidine group when compared with the propofol group (68.7% v 58.1%, p = 0.008) (Table 4, Fig 2). The mean postoperative time to extubation was also significantly reduced in the dexmedetomidine group compared with the propofol group (8.8 ± 16.5 hours v 12.8 ± 25.3 hours, p = 0.026) (Fig 3). A statistically significant difference in hospital LOS was observed in the dexmedetomidine group compared with the propofol group (181.9 ± 125.7 hours v 221.3 ± 226.8 hours, p = 0.001). ICU-LOS was also shortened in the dexmedetomidine group, although it failed to meet statistical significance (43.9 ± 41.0 hours v 52.5 ± 67.7 hours, p = 0.067) (Fig 4). In-hospital mortality occurred in 7 patients in the dexmedetomidine group (2.4%) and 3 patients in the propofol group (1%, p = 0.202). Average total hospital charges were \$3,994.73 less in the dexmedetomidine group. Average pharmacy charges were \$807.69 greater in the dexmedetomidine group.

The two sedation groups were stratified based on the type of procedure that each patient was undergoing. There were a total

Table 2. Baseline Co-morbidities

Co-morbidity	Dexmedetomidine (n = 291)	Propofol (n = 291)	p value
COPD	58 (19.9%)	55 (18.9%)	0.753
Heart Failure	45 (15.5%)	60 (20.6%)	0.106
Obesity (BMI ≥30)	114 (39.2%)	186 (63.9%)	0.079
Hypertension	191 (65.6%)	186 (63.9%)	0.364
OSA	20 (6.9%)	18 (6.2%)	0.737

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

Table 3. Operative Procedures

Procedure	Dexmedetomidine (n = 291)	Propofol (n = 291)	p value
Surgery Type	–	–	0.404
Valve Only	76 (26.1%)	63 (21.6%)	
CABG Only	179 (61.5%)	186 (63.9%)	
Valve & CABG	36 (12.4%)	42 (14.4%)	
Surgery Severity	–	–	0.001
Urgent	132 (45.4%)	176 (60.5%)	
Emergent	5 (1.7%)	7 (2.4%)	
Elective	154 (52.9%)	108 (37.1%)	

Abbreviation: CABG, coronary artery bypass graft.

of 139 valvular surgeries, 365 CABGs, and 78 combination CABG and valvular surgeries.

In the valvular surgery subgroup, 76 received dexmedetomidine and 63 received propofol. In the dexmedetomidine group 49 patients (64.5%) achieved early extubation, compared with the propofol group, in which 38 (60.3%) achieved early extubation. Average time to extubation was significantly decreased in the dexmedetomidine group compared with the propofol group (8.1 hours v 11.3 hours). Both hospital LOS and ICU-LOS also were shorter in the dexmedetomidine group compared with the propofol group (163.9 hours v 217.5 hours), (40.2 hours v 46.0 hours), respectively.

In the CABG subgroup, which accounted for most patients in this study, 179 patients received dexmedetomidine and 186 received propofol. In the dexmedetomidine group, 130 patients (72.6%) achieved early extubation, compared with the propofol group, in which 111 (59.7%) achieved early extubation. This was the largest difference in percentage of patients achieving early extubation in this study. Average time to extubation was significantly decreased in dexmedetomidine group compared with the propofol group (8.6 hours v 12.8 hours). Hospital LOS and ICU-LOS were also both shorter in the dexmedetomidine group compared with the propofol group (180.2 hours v 213.2 hours), (42.6 hours v 48.2 hours), respectively.

In the CABG with valvular procedure group, 36 received dexmedetomidine and 42 received propofol. In the dexmedetomidine group, 21 patients (58.3%) achieved early extubation, compared with the propofol group, in which 20 (47.6%) achieved early extubation. Average time to extubation was decreased in the dexmedetomidine group compared with the propofol group (11.5 hours v 15.0 hours). Both hospital LOS and ICU-LOS also were shorter in the dexmedetomidine group

Table 4. Main Results

	Dexmedetomidine (n = 291)	Propofol (n = 291)	p value	Confidence Interval
Early Extubation	200 (68.7%)	169 (58.1%)	0.008	1.59 (1.13-2.23)*
Time to Extubation (h)	8.8	12.8	0.026	
ICU LOS (h)	43.9	52.5	0.067	
Hospital LOS (h)	181.9	221.3	0.001	
In-hospital Mortality	7 (2.4%)	3 (1.0%)	0.202	

Abbreviations: ICU LOS, intensive care unit length of stay; LOS, length of stay.

* Unadjusted for surgical acuity.

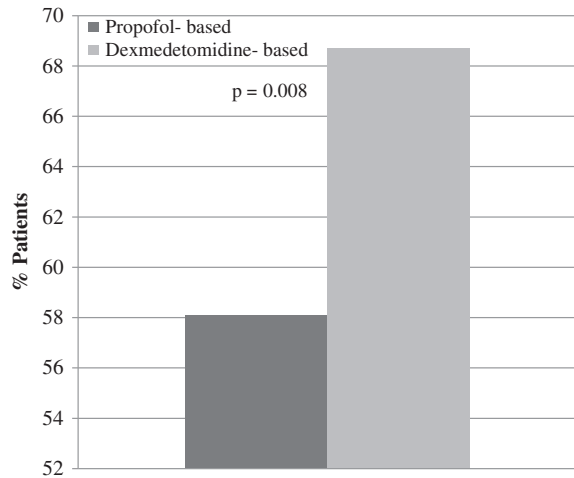


Fig 2. Cardiac surgery patients (%) achieving early extubation utilizing different sedation regimens. Propofol-based sedation, n = 291. Dexmedetomidine-based sedation, n = 291.

compared with the propofol group (228 hours v 262.9 hours), (58.4 hours v 81.0 hours), respectively.

DISCUSSION

Because of a nationwide propofol shortage, dexmedetomidine was utilized as the primary sedative in postoperative cardiac surgery patients at the study institution. The shift in sedative use at this institution enabled the authors to obtain a large group of dexmedetomidine patients to analyze. This study represents one of the largest retrospective analyses of patients receiving dexmedetomidine sedation after cardiac surgery.

When compared with patients who received propofol-based sedation, patients who received dexmedetomidine-based sedation after cardiac surgery had more favorable outcomes, including more frequent achievement of early extubation, decreased time to extubation, and a shorter hospital LOS. The most significant increase in achievement of early

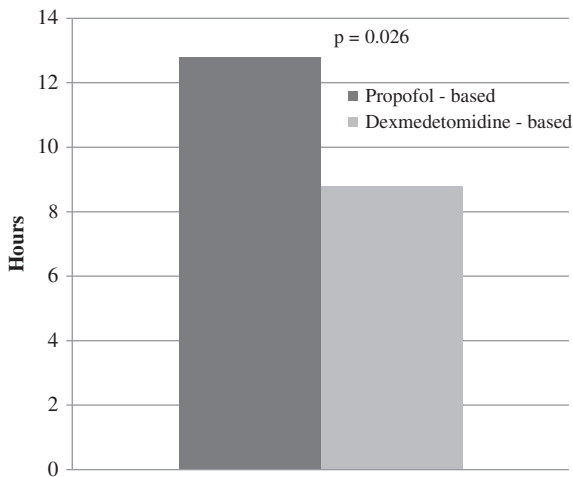


Fig 3. Average time to extubation (hours) of cardiac surgery patients utilizing different sedation regimens. Propofol-based sedation, n = 291. Dexmedetomidine-based sedation, n = 291.

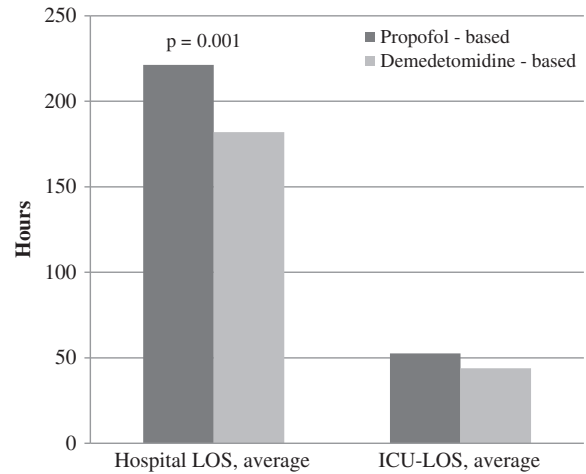


Fig 4. Average hospital length of stay (LOS) and intensive care length of stay (ICU-LOS), in hours, of cardiac surgery patients utilizing different sedation regimens. Propofol-based sedation, n = 291. Dexmedetomidine-based sedation, n = 291.

extubation was seen in patients who underwent a CABG in the dexmedetomidine group when compared with the propofol group; however, this benefit was seen across all groups of CABG, valvular, and combination surgeries. Safety of both agents was not directly analyzed in this study, but there were no significant differences in in-hospital mortality between the dexmedetomidine and propofol groups (2.4% v 1.0%, p = 0.202).

There were no significant differences in overall hospital charges between the two groups, and the total hospital charges in the dexmedetomidine group were less than those in the propofol group. Dexmedetomidine is more expensive than propofol, but the increased drug cost is likely mitigated by the reduction in both hospital and ICU-LOS. The cost analysis demonstrated that dexmedetomidine is not only a clinically beneficial sedative for postoperative cardiac surgery patients, but it also may be a cost effective alternative to propofol.

The results of this analysis are consistent with those of previous studies. In 2003, Herr et al compared levels of sedation, morphine use, and mean times to ventilator weaning and extubation after CABG surgery in patients receiving either dexmedetomidine-based or propofol-based sedation.² The primary outcome of this multicenter, randomized, prospective study was the efficacy of dexmedetomidine compared with propofol in achieving a goal level of sedation. Time to extubation was analyzed as a secondary outcome and was found to be similar between the two groups; however, the median time to extubation was decreased by approximately 1 hour in the dexmedetomidine group. The present study differs from the Herr et al study in that it was designed as an adequately powered, randomized, retrospective analysis with a primary objective of determining achievement of early extubation and decreased time to extubation. The Herr et al study's goal time to extubation was not specifically defined and likely varied between study sites. Both studies are representative of clinical practice use of the two sedatives. It should be noted that the use of dexmedetomidine in the Herr et al study

was limited to 24 hours of use and a maximum dose of 0.7 µg/kg/h, and this may not be indicative of current practices. Dosing and duration of therapies were not analyzed in the present study; however, sedation and analgesia were driven by a standardized order set for postoperative patients. On the basis of published findings, this institution uses a maximum dose of 1.5 µg/kg/h dexmedetomidine and limits the number of days of dexmedetomidine use to a maximum of 5 days.^{25,26}

In a recent 2011 study, Reichert et al evaluated the effects of substituting dexmedetomidine for propofol in 70 patients who underwent CABG surgery.²⁷ Their primary outcome evaluated opioid requirements in the first 12 hours after arrival to the ICU while secondary outcomes included the time to extubation and opioid requirements in the first 24 hours. The authors found no statistically significant differences between the propofol and dexmedetomidine-treated patients for either the primary or secondary outcomes. Given the small sample size of patients, it would have been very difficult to show a difference between the two groups. The present study included 582 patients and was adequately powered to show a 15% difference in achievement of early extubation. Another notable difference is that the present study included not only CABG surgery patients, but also patients undergoing a valve surgery with or without CABG.

The benefits of dexmedetomidine on achievement of early extubation when compared with propofol could be due to the lack of effect of dexmedetomidine on suppression of respiratory drive. Although not assessed by this study, other potential reasons for the benefits of dexmedetomidine sedation on early extubation include sympatholytic activity and decreased opiate requirements. Previous studies in surgical patients have shown decreased opiate requirements, supporting this claim.^{14,28}

There are several limitations to this study, some of which are intrinsic to its design as a single center, retrospective analysis. One significant limitation of this study was that dosing and duration of therapies was not measured. During the study period, the sedatives were documented in various places due to the implementation of computerized order entry and variations in the computer systems used. Also, duration of agents was unobtainable. The anesthetics utilized

in the OR remained the same for both groups. Induction agents included were methohexital, fentanyl, midazolam, and vecuronium. Anesthesia maintenance during cardiopulmonary bypass was with isoflurane, and either propofol or dexmedetomidine were initiated during bypass. All patients were assessed for extubation by respiratory and nursing protocols that did not change during the study period. Another limitation was the finding that a greater number of patients receiving dexmedetomidine underwent an elective procedure rather than an urgent procedure than those receiving propofol. No explanation can be offered; however, the definition of these procedures as urgent, emergent, or elective are somewhat subjective based on the patient's clinical course and are at the discretion of the staff member entering the data into the APOLLO database. It is unclear how the distribution of elective and urgent procedures affected the results of this study. For future studies, it may be beneficial to stratify groups based on severity of illness as defined through an APACHE II score or similar method. A limitation with the demographic data was that the patients' comorbidities, excluding obesity, were obtained from ICD-9 codes. Finally, conclusions about subgroups within the dexmedetomidine and propofol groups cannot be drawn from a statistical level of significance, as this study was only powered to analyze the primary objective of achievement of early extubation.

CONCLUSION

In this single-center retrospective analysis of effects of sedation on achievement of early extubation in postoperative cardiac surgery patients, dexmedetomidine-based sedation was found to have a statistically significant increase in achievement of early extubation over propofol-based sedation. Other clinical benefits of dexmedetomidine-based sedation over propofol-based sedation included a reduced time to postoperative extubation and a decreased hospital LOS. Dexmedetomidine-based and propofol-based sedation resulted in similar overall hospital charges. In summary, dexmedetomidine-based sedation had clinically beneficial effects in postoperative cardiac surgery patients.

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