Title
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Permalink
https://escholarship.org/uc/item/015237zd

Journal
Journal of cardiothoracic and vascular anesthesia, 30(6)

ISSN
1053-0770

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Publication Date
2016-12-01

DOI
10.1053/j.jvca.2016.02.026

Peer reviewed
The Effect of Dexmedetomidine on Outcomes of Cardiac Surgery in Elderly Patients

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Objective: The goal of this retrospective study was to investigate the effects of perioperative use of dexmedetomidine (Dex) on outcomes for older patients undergoing cardiac surgery.

Design: Retrospective investigation.

Setting: Patients from a single tertiary medical center.

Participants: A total of 505 patients (≥65 years old) who underwent coronary artery bypass graft (CABG) or valve surgery. CABG and/or valve surgery plus other procedures were divided into 2 groups: 283 received intravenous Dex infusion (Dex group) and 222 did not (Non-Dex group).

Interventions: Perioperative Dex intravenous infusion (0.24 to 0.6 μg/kg/h) initiated after cardiopulmonary bypass and continued for <24 hours postoperatively in the ICU.

Measurements and Main Results: Data were risk adjusted, propensity score weighted, and multivariate logistic regression was used. The primary outcome was mortality. Secondary outcomes included postoperative stroke, coma, renal failure, and sepsis. Perioperative Dex infusion significantly decreased in-hospital mortality (0.90% vs. 2.83%; adjusted odds ratio [OR], 0.099; 95% confidence interval [CI], 0.030-0.324; p = 0.004) and operative mortality (1.35% vs. 3.18%; adjusted OR, 0.251; 95% CI, 0.077-0.813; p = 0.021). Perioperative Dex treatment also reduced the risk of stroke (0.90% vs. 1.77%; adjusted OR, 0.15; 95% CI, 0.038-0.590; p = 0.007), and delirium (7.21% vs. 10.95%; adjusted OR, 0.35; 95% CI, 0.212-0.578; p < 0.0001).

Conclusions: Results from this study (ClinicalTrials.gov identifier: NCT01683448) suggested perioperative use of dexmedetomidine was associated with decreases in in-hospital and operative mortality in elderly patients following cardiac surgery. It also reduced incidences of postoperative stroke and delirium in elderly patients.

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KEY WORDS: dexmedetomidine, elderly cardiac surgery, outcome operative mortality, hospital mortality

INTRODUCTION

Cardiovascular disease is the most common cause of death in the elderly population. With the advancement of technology, cardiac surgery is feasible in elderly patients with acceptable risks. Currently, more than 67% of patients presenting for cardiac surgery are older than 65 years and have increased comorbidities.1 Cardiovascular, pulmonary, and renal diseases are more common and contribute to greater perioperative complications, and this may influence perioperative outcomes in patients with advanced age.2 Elderly high-risk patients usually require prolonged intensive care unit (ICU) stays and are at an increased risk for mortality and morbidity.3-5 It is well known that surgical stress and cardiopulmonary bypass (CPB) can increase plasma levels of norepinephrine and epinephrine. Dexmedetomidine (Dex) is a highly selective α2-adrenergic agonist that strongly modulates the activity of the sympathetic nervous system by binding to the α2-receptors present in both the central and peripheral nervous systems and inhibiting the release of norepinephrine, thus modulating sympathetic activity.6,7 Because of this, Dex has been used extensively in the ICU as a sedative and during surgery as an adjuvant anesthetic to attenuate perioperative hemodynamic abnormalities. Multiple studies have demonstrated that Dex has a protective effect on the heart, brain, and kidneys.8-11 It was associated with decreased mortality, time to extubation, and hospital length of stay (LOS) in cardiac surgical patients.12-15 The authors previously have published a study describing the effects of Dex on outcomes of patients undergoing cardiac surgery.12 In that study, Dex reduced in-hospital, 30-day, and 1-year mortality and decreased the incidences of postoperative complications and delirium. Portions of these data also were used in the study published in the Journal of Cardiothoracic and Vascular Anesthesia, which found that Dex infusion during coronary artery bypass graft (CABG) surgery was more likely to achieve improved in-hospital, 30-day, and 1-year survival rates, and a significantly lower incidence of delirium.15 The authors now report the results of another study using the same database. The aim of this subanalysis was to investigate the effects of perioperative use of Dex on outcomes for older patients undergoing cardiac surgery.

METHODS

Study Design

After obtaining local Institutional Review Board approval, all patients (≥65 years old) who underwent cardiac surgery with CPB at the UC Davis Medical Center from January 1, 2006 to December 31, 2011 were entered into the study. This study was a single-center, retrospective cohort study involving 561 consecutive patients. Patients in this study met the criteria for the use of Dexmedetomidine (Dex) during their current study period. The authors now report the results of another study using the same database. The aim of this subanalysis was to investigate the effects of perioperative use of Dex on outcomes for older patients undergoing cardiac surgery.

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Funding: This work was supported by the Department of Anesthesiology and Pain Medicine, the Department of Surgery, and the Department of Internal Medicine of University of California Davis Health System and NIH grant UL1 TR000002 of the University of California Davis Health System. This work was also supported by grants from the National Natural Science Foundation of China NO 81471835 and NO 81471889.

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1053-0770/2016-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2016.02.026
following criteria: CABG or valve surgery, or CABG or valve surgery combined with other procedures (Maze operation). Patients excluded from this study were those undergoing emergency surgery, off-pump or robotic surgery, surgery demanding deep hypothermic circulatory arrest, or surgery involving the thoracic aorta (Fig 1). A total of 505 patients met the inclusion criteria and were divided into 2 groups: those who used Dex (Dex group; n = 222, 43.96%) and those who did not use Dex (Non-Dex group; n = 283, 56.04%) in surgery (Fig 1).

Data Collection

The patient data were collected and organized following the template of the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database and the hospital medical records, which included demographics, patient past medical and surgical histories, preoperative risk factors, preoperative medications, intraoperative data, postoperative stroke, coma, myocardial infarction (MI), heart block, cardiac arrest, acute renal failure, dialysis required, and in-hospital, operative, and 1-year all-cause mortality. Data were collected independently as part of the STS database on each patient during the course of the hospitalization. After routine monitoring, general anesthesia was induced with midazolam, lidocaine, propofol or etomidate, fentanyl, and rocuronium, maintained with sevoflurane. Ventilation with 50% oxygen in air was controlled to an end-tidal CO₂ of 35 to 45 mmHg by adjustment of tidal volume and respiratory rate. Arterial catheter, pulmonary artery catheter, and transthoracic echocardiography were used as hemodynamic and cardiac function monitoring after anesthesia induction. Perioperative Dex administration was defined as an intravenous infusion (0.24 to 0.6 μg/kg/h) initiated after CBP and continued for <24 hours postoperatively in the ICU. The infusion rate of Dex was adjusted according to the patients’ hemodynamic changes in response to stimulation.

Major and Secondary Outcomes

Major outcomes of this study were in-hospital, operative, and 1-year mortality. Secondary outcomes included postoperative permanent or transient stroke, coma, MI, heart block, cardiac arrest, renal failure or new dialysis requirement, delirium, postoperative length of mechanical ventilation, length of ICU stay, LOS, and 30-day readmission. On the basis of the STS criteria, the following definitions were used. Permanent stroke was defined as a postoperative stroke (any confirmed neurologic deficit of abrupt onset caused by a disturbance in blood supply to the brain) that did not resolve within 24 hours. Transient ischemic attack was defined as a loss of neurologic function that was abrupt in onset but with complete return of function within 24 hours. The definition of coma was a new postoperative coma that persisted for at least 24 hours secondary to anoxic/ischemic or metabolic encephalopathy, thromboembolic event, or cerebral bleed. Cardiac arrest included one of the following: (a) ventricular fibrillation; (b) rapid ventricular tachycardia with hemodynamic instability; (c) asystole; (d) implantable cardioverter-defibrillator shocks. Heart block was defined as a new-onset block requiring the implantation of a permanent pacemaker of any type before discharge. The STS definition of postoperative renal failure was used to determine postoperative acute kidney injury (AKI). This definition included the highest Cr level recorded in the postoperative course that was ≥3-fold baseline Cr or Cr ≥4 with an acute increase of ≥0.5mg/dl or new requirement for postoperative dialysis. Finally, sepsis was defined as a systemic inflammatory response syndrome when at least two of the following criteria were present: hypothermia or hyperthermia (≥38.5 or <36.0°C), tachycardia or bradycardia, tachypnea, leukocytosis or leukopenia, or thrombocytopenia. Delirium was defined as illusions, confusion, and cerebral excitement during the hospital stay and having a comparatively short course. Any complication included all postoperative events occurring during the hospitalization, including the entire postoperative period up to discharge, even if >30 days.

Statistical Methods

Continuous variables were assessed as mean ± standard deviation and compared by use of the t-test; categorical variables were reported as percentages and compared by use of the χ² test (2-tailed). Univariate and multivariate logistic regressions were performed to evaluate the associations of demographic, therapeutic, and clinical outcome variables. To decrease selection bias in patients who received Dex administration, the authors computed the propensity score, that is, the
conditional probability of each patient receiving Dex, with a multivariable logistic regression model that included patient demographic and clinical risk factors (Table 1).

The multivariate model analysis used to assess any complication included Dex use, age, gender, status of the procedure, smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, family history of coronary artery disease (CAD), dyslipidemia, hypertension, MI, congestive heart failure, surgery type, and perfusion time. The multivariate model assessing delirium included Dex use, age, gender, body mass index (BMI), cerebrovascular disease, family history of CAD, dyslipidemia, ejection fraction, and surgery type. The multivariate model used to assess stroke included Dex use and surgery types. The multivariate model used to assess in-hospital mortality included Dex use and surgery types. The multivariate model used to assess operative mortality included Dex use and status of the procedure (urgent vs elective). The multivariate model used to assess 1-year mortality included Dex use, age, status of the procedure, chronic lung disease, diabetes, MI, renal failure, last creatinine level, dyslipidemia, intra-aortic balloon pump (IABP), and perfusion time.

To achieve model parsimony and stability, the backward selection procedure was applied, with a dropout criterion of \( p > 0.1 \). The candidate risk factors were selected on the basis of the literature reviews, clinical possibility, and variables collected in the database. The candidate independent variables included age, sex, race, status of the procedure, BMI, creatinine level, smoking, chronic lung disease, cerebrovascular disease (CVD), peripheral vascular disease (PVD), family history of CAD, diabetes mellitus, hypertension, hypercholesterolemia, dyslipidemia, renal failure, IABP, \( \beta \)-blockers, nitrates, angiotensin-converting enzyme inhibitors (ACEI), adenosine diphosphate (ADP) inhibitors, glycoprotein IIb/IIIa inhibitors, coumadin, inotropes, aspirin, lipid-lowering drugs, surgery type, ejection fraction, perfusion time, cross-clamp time, and year of surgery. The parsimonious multivariable propensity model for Dex infusion included emergency status of patients, preoperative CVD, preoperative PVD, preoperative dyslipidemia, preoperative congestive heart failure, surgery type, and year of surgery (Fig 2). Then the authors created a propensity-weighted logistic regression model for 1-year mortality. The C statistic was reported as a measure of predictive power. The authors compared the propensity-weighted and risk-adjusted 1-year mortality between the cohort with Dex use and with no Dex use. The results are reported as percentages and odds ratios (OR) with corresponding 95% confidence intervals (CI). A parsimonious Cox proportional hazards model was created to estimate the effect of Dex for 1-year survival. All reported \( p \) values were 2-tailed, and values of \( p < 0.05 \) were considered to be statistically significant. All statistical analyses were performed with SAS version 9.3 for Windows (SAS Institute, Cary, NC).

### RESULTS

#### Baseline and Intraoperative Parameters

The demographic and clinical data are presented in Table 1. There were no significant differences between the two groups with respect to age, sex, race, medical history (smoking, chronic lung disease, PVD, family history of CAD, diabetes mellitus, hypertension, MI, ejection fraction, or last creatinine level) and preoperative medical therapy (ACEI, \( \beta \)-blockers, ADP inhibitors, nitrates, coumadin, inotropes, glycoprotein IIb/IIIa inhibitor, or aspirin). However, the patients in the Dex group presented with a greater incidence of renal failure (4.5\% vs 0.7\%, \( p = 0.005 \)), congestive heart failure (38.3\% vs 6.7\%, \( p < 0.0001 \)), dyslipidemia (66.2\% vs 54.8\%, \( p = 0.009 \)), and the use of lipid-lowering medications (66.7\% vs 56.5\%, \( p < 0.0001 \)). The patients in the Dex group presented with a lower BMI (28.3\% vs 29.7\%, \( p = 0.02 \)), less urgent surgery (45.5\% vs 58\%, \( p = 0.005 \)), and lower incidence of CVD (21.6\% vs 29.7\%, \( p = 0.041 \)).

#### Procedural Characteristics

In terms of surgery types, CABG only (45.5\% vs 53.4\%, \( p < 0.0001 \)) was less frequent and valve/valve + other (21.6\% vs 29.7\%, \( p = 0.005 \)) was less common.
6.7%, p < 0.001) were more frequent in the Dex group. CBP time (181.7 ± 61.2 v 203.7 ± 79.4 minutes; p = 0.001) and aortic cross-clamp time (129.2 ± 50.8 v 141.9 ± 58.9 minutes; p = 0.009) were significantly shorter and the incidence of perioperative IABP use (5% v 13.1%; p = 0.002) was significantly lower in the Dex group (Table 2).

Table 2. Procedural Characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dex (n=222)</th>
<th>Non-Dex (n=283)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion time, min</td>
<td>181.7 (61.2)</td>
<td>203.7 (79.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>129.2 (50.8)</td>
<td>141.9 (58.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>IABP used, n (%)</td>
<td>5 (5.0)</td>
<td>37 (13.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgery type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG only</td>
<td>101 (45.5)</td>
<td>151 (53.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG+valve+(other)</td>
<td>61 (27.5)</td>
<td>93 (32.9)</td>
<td>0.192</td>
</tr>
<tr>
<td>CABG+other</td>
<td>12 (5.4)</td>
<td>20 (7.1)</td>
<td>0.447</td>
</tr>
<tr>
<td>Valve+(valve+other)</td>
<td>48 (21.6)</td>
<td>19 (6.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NOTE. Values are n (%) for categorical variables and mean ± SD for continuous variables.

Abbreviations: CABG, coronary artery bypass graft; Dex, dexmedetomidine; IABP, intra-aortic balloon pump; SD, standard deviation.

Postoperative Complications and Mortality

Univariate analysis demonstrated that 11 out of the total of 505 patients (2.18%) died in the hospital, 12 patients (2.37%) died during surgery, and 39 patients (7.72%) died within 1 year. In-hospital, operative, and 1-year mortality were 0.9%, 1.35%, and 7.21%, respectively, in the Dex group and were 2.83%, 3.18%, and 8.13% in the Non-Dex group. Total length of ICU stay (142.5 ± 191.5 v 106.2 ± 132.8 hours, p = 0.017) was longer in the Dex group. Between the two groups, no differences were seen in the incidence of postoperative complications: MI, coma, heart block, cardiac arrest, delirium, renal failure, sepsis, ventilation time, or LOS, readmission within 30 days, in-hospital, operative, and 1-year mortality (Fig 3).

One-Year Mortality

After risk adjustment, a Cox proportional hazards model analysis revealed that older age, urgent surgery, preoperative last creatinine level, and perfusion time significantly increased the 1-year mortality; Dex was no longer a contributing factor for the 1-year survival rate (Fig 4).

DISCUSSION

This was a subanalysis using the data the authors used before12 to investigate the effect of Dex on outcomes for the elderly cardiac surgery population. The current study found that perioperative Dex use significantly reduced in-hospital and
operative mortality and was associated with improved early survival rates in elderly patients undergoing cardiac surgery. The authors’ results further suggested that perioperative intravenous Dex was associated with a reduced incidence of postoperative stroke and delirium after cardiac surgery. Perioperative Dex infusion may affect the mortality rates in elderly cardiac surgical patients. Age has been suggested as an independent risk factor for cardiac surgery outcomes. Frilling and colleagues found that in-hospital mortality in geriatric patients undergoing aortic valve replacement (AVR) was 2.56% in isolated valve replacement and 3.38% in patients who had additional bypass surgery. The authors’ results revealed the in-hospital mortality (2.83%) and operative mortality (3.18%) in the Non-Dex group was similar to the previous reports (2%-4.4%). However, in-hospital (0.9%) and operative mortality (1.5%) were significantly lower in patients who received Dex. The 1-year total mortality was 7.72%; that was similar to the other published study. Barreto-Filho and colleagues found that 30-day and 1-year mortality were 3.5% and 9.9% in isolated AVR versus 5.1% and 12.3% in AVR with concomitant CABG, respectively. The authors of this study found that although in-hospital and operative mortality rates were lower in the Dex group, there were no statistical differences in 1-year mortality (7.21% vs 8.13%, p = 0.878) between the two groups. Dex was no longer a contributing factor in the Cox proportional hazards analysis as to the 1-year survival rate, which differed from the other study. Thus, perioperative Dex use may be associated with an improved short-term survival rate but did not improve the 1-year survival rate in older cardiac surgical patients.

Stroke is a devastating complication following cardiac surgery and it has been reported that the prevalence of stroke was 1.6 to 5.25% among patients undergoing different cardiac surgeries. Dex, a highly selective α2-adrenoceptor agonist, provides sedation, sympatholysis, and analgesia without respiratory depression. In the current study, Dex use decreased the incidence of postoperative stroke after risk adjustment. The exact cause of stroke after surgery is understood poorly. A preclinical study showed significant neurologic improvement in Dex-treated animals following stroke. The neuroprotective effect of Dex was suggested to be mediated by activation of the α2A-adrenergic receptor subtype that modulates neurotransmitter release in the central and peripheral sympathetic nervous systems. Microembolization produced during CPB, O2 supply/demand imbalance, and the systemic inflammatory response may be contributing factors. Chi and colleagues suggested Dex could improve microregional O2 supply/consumption balance and may have contributed to the decreased size of cortical infarction in the early stage of reperfusion in an animal study.

Postoperative delirium is common among older patients undergoing cardiac surgery. The incidence of postoperative delirium was reported to range from 30% to 55% in elderly patients undergoing cardiac surgery. The authors of this study also
found that those who received Dex had a significantly lower incidence of delirium after cardiac surgery. At the same time, the authors observed the prevalence of delirium in the present study was lower than most reported results. The reason may have been that the authors included only patients with hyperactive delirium in this database; many patients with hypoactive delirium were therefore likely to be undetected. A study had shown that hypoactive delirium was the most common motor subtype in geriatric patients. Pandharipande and colleagues found hyperactive delirium in no more than 1% of surgical ICU patients, whereas the majority of patients had hypoactive (64%) delirium in the postoperative period. On the other hand, delirium assessment is somewhat subjective and may be susceptible to observational bias. A study showed that Dex could provide neurocognitive protection in an animal model. In a retrospective cohort study, use of Dex was associated with a decrease in postoperative AKI, particularly in patients with normal preoperative kidney function or mild chronic kidney disease. However, the authors’ data failed to show the relationship between the use of Dex and the reduction of AKI in the aged population.

In a randomized trial, Dex-treated patients spent less time on the ventilator. A meta-analysis confirmed the results. The mean postoperative time to extubation and length of hospital stay were shorter in the Dex group when compared with the propofol group, and Dex-based sedation resulted in achievement of early extubation more frequently than propofol-based sedation. In this study, while durational mechanical ventilation was shorter in the Dex-treated patients, the ICU length of stay was longer; it was different from the other studies. However the length of hospital stay did not differ between the two groups. The reason for the discrepancy in the results was unclear. Further studies to confirm this result are needed.

There were several limitations of this study. This was a single-center, observational cohort study. Multivariate regression in combination with propensity score adjustments were applied to this study population to reduce the bias; however, the potential confounding bias associated with a nonrandomized study remains. The sample size of this study was relatively small. Further prospective, multicenter, randomized, and controlled studies with a larger sample size are required to confirm the effects in this study.

CONCLUSIONS

The retrospective analysis demonstrated that elderly cardiac surgical patients who received Dex after CPB surgery had better in-hospital and operative survival rates. Perioperative use of Dex also was associated with significant decreases in the incidences of postoperative stroke and delirium. A prospective, randomized, multicenter study focused on the use of dexmedetomidine in elderly cardiac surgery patients is indicated to confirm these findings.

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