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ORIGINAL RESEARCH ARTICLE

Clinical and Economic Impact of Substituting Dexmedetomidine for Propofol due to a US Drug Shortage: Examination of Coronary Artery Bypass Graft Patients at an Urban Medical Centre

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Abstract

Background Propofol has reduced healthcare costs in coronary artery bypass graft (CABG) surgery patients by decreasing post-operative duration of mechanical ventilation. However, the US shortage of propofol necessitated the use of alternative agents.

Objective This study sought to evaluate clinical and economic implications of substituting dexmedetomidine for propofol in patients undergoing CABG surgery.

Methods This was a retrospective cohort study. Patients undergoing isolated, elective CABG surgery and sedated with either propofol or dexmedetomidine during the study period were included. The cohorts were matched 1:1 based on important characteristics. The primary outcome was the number of patients achieving a post-operative duration of mechanical ventilation ≤6 h. Secondary outcomes were post-operative intensive care unit (ICU) length of stay (LOS) ≤48 h, total post-operative LOS ≤5 days, the need for adjunctive opioid therapy and associated cost savings. Variables recorded included patient demographics, comorbid medical conditions, health risks, sedation drug doses, post-operative medical complications and sedation-related adverse events. Univariate and multivariate analyses were completed to examine the relationship between these covariates and post-operative LOS. The cost analysis consisted of examination of the net financial benefit (or cost) of choosing dexmedetomidine versus propofol in the study population, with utilisation observed in the study converted to costs using institutional data from the Premier database.

Results Eighty-four patients were included, with 42 patients per cohort. Mechanical ventilation duration ≤6 h was achieved in 24 (57.1 %) versus 7 (16.7 %) in the dexmedetomidine and propofol cohorts, respectively ($p < 0.001$). More patients treated with dexmedetomidine achieved ICU LOS ≤48 h ($p < 0.05$) and total hospital LOS ≤5 days ($p < 0.05$), as compared with the propofol group. Multivariate analysis revealed that having one or more post-operative medical complication was the most significant predictor of increased post-operative LOS, whereas choosing dexmedetomidine was also significant in terms of reduced post-operative LOS. The estimated net financial benefit of choosing dexmedetomidine versus propofol was US$2,613 per patient (year 2012 value).

Conclusions Findings suggest that use of dexmedetomidine as an alternative to propofol for sedation of CABG patients post-operatively contributes to reduced mechanical ventilation time, ICU LOS and post-operative LOS. Higher drug costs resulting from the propofol shortage were offset by savings in post-operative room and board costs. Additional savings may be possible by preventing medical complications to the extent possible.

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Key Points for Decision Makers

- Clinical and economic data supporting the use of alternative agents for sedation for coronary artery bypass graft surgeries are needed, especially in the current environment of drug shortages.
- Propofol therapy may be associated with more post-operative complications due to pharmacodynamic properties and formulation characteristics leading to inferior clinical outcomes compared with dexmedetomidine.
- Increased drug costs of dexmedetomidine therapy can be offset by cost savings derived from the decreased length of stay compared with propofol.
- Dexmedetomidine potentially provides, at minimum, marginal clinical benefit over propofol, which should be the primary factor in clinical decision making, particularly if the cost of dexmedetomidine diminishes when its patent expires.

1 Background

Since the 1990s, fast-track cardiac anaesthesia (FTCA), a strategy to facilitate early extubation and subsequent discharge from the intensive care unit (ICU) utilising small doses of short-acting opioids and propofol or volatile anaesthetics, has displaced traditional anaesthetic and sedation regimens as the current standard of care throughout the world [1, 2]. The growing disparity between the volume of patients requiring cardiac surgery and limited intensive care resources created economic pressures that forced this paradigm shift in protocols [1, 3]. Ideally, FTCA maximises efficient resource utilisation and cost savings by not only minimising mechanical ventilation but also minimising post-operative complications reducing ICU and overall hospital length of stay (LOS) [4, 5]. Despite the growing literature on anaesthetic and sedative interventions during cardiac surgery, evidence pertaining to the effectiveness and costs of FTCA is still emerging.

Past studies have demonstrated reductions in total healthcare costs in patients receiving propofol for FTCA without an increased incidence of post-operative complications [1–5]. Pharmacological advantages of propofol for FTCA include quick onset and short duration of action, allowing for ease of titration and more rapid arousal for weaning and endotracheal extubation [6, 7]. Additionally, the cost of propofol is considerably lower than other sedative agents. However, propofol lacks analgesic activity, thus requiring adjunctive opioid therapy. More importantly, propofol can cause significant respiratory depression, potentially augmenting the adverse effects of opioid analgesics [6–8].

The convergence of several events triggered a US propofol shortage crisis that began in 2009. Prior to 2009, there were three manufacturers supplying propofol to the US market. In late 2009, two of the manufacturers implemented significant recalls (one due to microbial contamination, the other due to particulate matter contamination) [9]. The shortage reached a peak in mid-2010 when one of the two manufacturers announced it was permanently discontinuing propofol production, and the other manufacturer expanded its recall [9]. At that time, healthcare purchasers were scrambling to allocate scarce supplies and identify therapeutic alternatives. In an attempt to alleviate the shortage, the US FDA issued a temporary allowance for re-importation of a propofol product approved in other countries [9]. Although the propofol shortage had abated by October 2011, long-term concerns about the propofol supply persist, because the complicated and expensive production requirements of the drug may pose continued challenges to manufacturers [10].

One of the strategies adopted during the shortage was use of dexmedetomidine as an alternative to propofol in certain patients. Since the effects of dexmedetomidine are not mediated by γ-aminobutyric acid (GABA), dexmedetomidine does not depress the respiratory drive and exhibits analgesic-sparing effects [6, 7]. Consequently, sedation with dexmedetomidine purportedly reduces the need for additional opioid analgesic therapy and expedites extubation. However, these effects have not been conclusively demonstrated due to conflicting reports in the literature [8, 11]. Despite this lack of evidence, a previous retrospective outcomes analysis revealed significant cost savings when dexmedetomidine was added to midazolam and propofol [11].

Dexmedetomidine has been proposed as a safe and effective substitute for propofol in the coronary artery bypass graft (CABG) surgical population [8]. Dexmedetomidine use in the cardiac surgery population at our institution has persisted despite its higher acquisition costs. To better understand the implications of using dexmedetomidine as an alternative to propofol in the management of patients undergoing elective CABG, we conducted this study examining both clinical and economic outcomes (inpatient utilisation and costs). In addition, we examined the extent to which the choice of these two agents predicts inpatient utilisation (measured as post-operative LOS). The analysis was performed from the perspective of our large (900 bed) academic tertiary care medical centre located in metropolitan Philadelphia.

2 Methods

This retrospective cohort study was approved by the institutional review board at Thomas Jefferson University

Hospital (TJUH) (Philadelphia, PA, USA) with a waiver for informed consent. The analytic sample was identified through the Society of Thoracic Surgery database and cross-referenced with the University HealthSystem Consortium database through MS-DRG (diagnosis-related group) codes to identify patients that underwent isolated, elective CABG surgeries at TJUH during the appropriate timeframes. Patient-level data (clinical and utilisation measures) for these individuals were obtained from paper and electronic charts. Patients were included if they were older than 18 years and underwent an isolated, elective CABG surgery at our institution between January 2008 and December 2011. Propofol- and dexmedetomidine-treated patients were considered for inclusion in the study if their surgery occurred from January 2008 to March 2010 and October 2010 to December 2011, respectively. The gap between these two timeframes represents a transition period in which sedation regimens primarily consisted of fentanyl and midazolam. Cardiac surgery ventilator weaning protocols for dexmedetomidine and propofol were consistent across the study period.

Patients were excluded from this study if they had received crossover sedation (defined as sedation with propofol or dexmedetomidine with conversion to the other agent during the post-operative period), had any concurrent neurological abnormalities, received an off-pump CABG, received any additional surgical interventions, or had an incomplete medical record. The two treatment groups were matched 1:1 based on age, gender, number of grafts and cardiopulmonary bypass (CPB) time—variables hypothesised to contribute significantly to study outcome measures.

Pertinent patient characteristics captured from charts included age, gender, height, body weight, body mass index (BMI), left ventricular ejection fraction, and history of alcohol, benzodiazepine or opioid analgesic use. Perioperative variables of interest were CPB time, number of vessels bypass, and total time from sternal opening to closure. Post-operative variables recorded were sedation drug therapy used (propofol or dexmedetomidine), including total cumulative dose and mean dosage rate (per hour for dexmedetomidine and per minute for propofol); time of ICU admission, discharge and extubation; total amount of opioid analgesics administered; and need for rescue sedation with benzodiazepines. Pain scores were reported on the 10-point Numeric Rating scale (0 = no pain, 10 = worst pain) and sedation was titrated to achieve a score of −1 (drowsy) to −3 (moderate sedation) on the Richmond Agitation Sedation Scale (RASS). Post-operative medical complications occurring during the stay (stroke, acute renal failure, prolonged mechanical ventilation, mediastinal infection, atrial fibrillation, myocardial infarction, re-operation following initial procedure) were recorded, as were major adverse events related to sedation drug therapy (hypotension, defined as mean arterial pressures less than 65 mmHg and bradycardia, defined as heart rate less than 60 beats per minute).

Utilisation measures (extubation time, post-operative ICU LOS and total post-operative LOS) were analysed as continuous variables using non-parametric methods (Mann-Whitney *U*) in accordance with right-skewed distributions. Secondarily, we recoded these utilisation measures to examine them based on cut points meaningful to the institution. For extubation time, our categorical variable was patients successfully extubated within 6 h from the start of mechanical ventilation, i.e. duration of mechanical ventilation ≤6 h. This measure was selected based on the goal duration of mechanical ventilation established by the institution's cardiothoracic surgery practice and as defined by Cheng et al. [12]. LOS variables were categorised as follows: post-operative ICU LOS ≤48 h, and post-operative hospital LOS ≤5 days; these LOS goals are established as a part of the institution's clinical pathway and are consistent with previously reported LOS in this population [13]. Categorical variables were examined using chi-square testing. Multivariable linear regression analysis (backwards elimination regression model) was used to examine the extent to which sedation drug choice (dexmedetomidine vs. propofol) predicts inpatient utilisation. For this analysis, the dependent variable was defined as post-operative LOS (days), which we considered to be the most relevant of the utilisation variables measured. Though the two study cohorts were statistically matched, we chose to perform a multivariate analysis to explore whether covariates such as adverse events influenced post-operative LOS. Independent variables included these adverse events as well as patient demographics (age, gender), medical history, health risks, clinical variables, post-operative medical complications, sedation drug received (in the model, the sedation drug was set as dexmedetomidine), and adverse events during sedation therapy (bradycardia, hypotension). Due to the small number of patients experiencing the individual types of post-operative medical complications, these were included in multivariate analyses based on having one or more of the captured events. All analyses were completed using SPSS® version 19 (IBM Corp., Armonk, NY, USA).

The cost analysis consisted of examination of the net financial benefit (or cost) of choosing dexmedetomidine versus propofol in the study population. Since the institution is typically paid via a case rate for CABG patients, the primary goal of the cost calculation was to estimate, on a per patient basis, whether the additional drug costs of dexmedetomidine were offset by savings in total post-operative room and board costs. Therefore, the formula used to calculate net financial benefit (or cost) was as follows:

$$\text{Net financial benefit (or cost)} = (C_i + C_t) - C_d$$

where C_i is the mean per person ICU room and board costs, C_t is the mean per person post-ICU telemetry room and board costs, and C_d is the mean per person costs of sedation drug therapy (i.e. propofol or dexmedetomidine) during mechanical ventilation.

Calculation of net financial savings required converting ICU LOS, post-ICU telemetry room LOS and sedation drug utilisation to dollars (US$; year 2012 values). Conversion factors were obtained from the Premier database for the first quarter of fiscal year 2011 at the institution. The Premier database is available from Premier Inc. (Charlotte, NC, USA), and contains clinical and utilisation data from more than 600 hospitals and ambulatory centres [14]. Specific conversion factors were as follows: ICU room and board cost per day US$1,999; telemetry room and board cost per day US$1,497, drug acquisition costs were obtained from the institution's distributor; per unit pricing was US$0.367/μg for dexmedetomidine and US$0.0113/mg for propofol. Sensitivity analyses were not performed since the study was intended to inform decision makers about findings specific to our institution.

3 Results

Eighty-four patients were included in this study, with 42 patients in each cohort (dexmedetomidine, propofol). Baseline demographic and operative characteristics were not statistically different between the two groups, indicating successful matching (Table 1). The mean total ventilation dose for dexmedetomidine was 398 μg with a mean dose rate of 0.5 μg/kg/h. The total ventilation dose of propofol was 2,613 mg with a mean dose rate of 35 μg/kg/min. Average RASS scores were maintained between −1 and −3 in both cohorts indicating adequate levels of sedation achieved with each of the two drug treatments.

Outcome measures are reported in Table 2. Analysis of continuous variables indicated a mean duration of mechanical ventilation was 11.8 h in the dexmedetomidine cohort versus 22.6 h in the propofol cohort ($p < 0.01$). In the dexmedetomidine group, mean time to discharge from ICU was 54.0 h (2.3 days) versus 78.0 h (3.3 days) in the propofol group ($p = 0.055$). Mean post-operative total LOS in the dexmedetomidine cohort was 6.0 versus 7.5 days for those patients in the propofol cohort ($p = 0.062$).

Analysis of categorical variables indicated that a mechanical ventilation duration ≤6 h was achieved in 24 (57.1 %) of those in the dexmedetomidine cohort, versus seven (16.7 %) in the propofol cohort ($p < 0.001$). Similarly, 34 (81.0 %) of the patients receiving dexmedetomidine were discharged from the ICU in ≤48 versus 24 h (57.1 %) of the patients on propofol ($p < 0.05$), and 25 (59.5 %) of the dexmedetomidine group had a post-operative hospital LOS ≤5 days, as compared with 16 (38.0 %) in the propofol group ($p < 0.05$). Additional opioid requirements were 320 and 699 μg of fentanyl equivalents in the dexmedetomidine and propofol arms, respectively ($p = 0.538$). Significantly higher doses of midazolam were required in the dexmedetomidine arm than propofol (1.1 vs. 0.1 mg; $p = 0.008$). Rates of post-operative medical complications and sedation-related adverse events were similar between the treatment groups (Table 2).

The results of the multivariable regression model are shown in Table 3. Having one or more medical complication was the most significant predictor of post-operative LOS ($p = 0.008$), with sedation drug choice also significant ($p = 0.047$) when accounting for other relevant variables. Neither of the two sedation drug adverse events (hypotension, bradycardia) were significant, nor were patient demographics, medical history or other clinical covariates (number of vessels diseased, BMI).

Cost findings are shown in Table 4. While mean per patient sedation therapy costs were higher for dexmedetomidine, post-operative ICU and telemetry days were lower than for propofol, translating to room and board savings. The net financial benefit of choosing dexmedetomidine versus propofol sedation in the study population was US$2,632 per patient (Table 4).

4 Discussion

Drug shortages have gained increased global attention in recent years. In the US, the number of drug shortages has steadily risen since the early 2000s [15]. Drug shortages are concerning because they not only may compromise the quality of care, but also because they result in unanticipated increases in drug expenditures. While published data have estimated the unanticipated drug spending due to shortages, this is the first known published study to examine the issue by measuring the clinical impact more broadly as well as cost offsets elsewhere. The propofol shortage we investigated in this study primarily resulted in a substitution with dexmedetomidine, and this switch reduced overall hospital costs and improved patients' clinical outcomes. Our findings suggest that, in some cases, drug shortages may actually provide an opportunity to positively affect patient care. Thus, in addition to mitigating the logistical and budgetary challenges of shortages, hospital decision makers should broadly consider the impact of strategies to address shortages, such as therapeutic interchanges.

Through its activity as a highly specific α_2-agonist, sedation with dexmedetomidine purportedly reduces the need for additional opioid analgesic therapy and expedites

Table 1 Baseline characteristics of the coronary artery bypass graft patients sedated on dexmedetomidine and propofol in matched patient cohorts ($n = 84$)

Characteristics	Dexmedetomidine ($n = 42$)	Propofol ($n = 42$)
Demographics		
Age (mean years)	64.1	64.2
Male (%)	90.5	90.5
CPB time (mean minutes)	80.8	82.9
Clinical variables		
Diseased cardiac vessels (mean number)	2.9	2.9
LVEF (mean %)	54.1	46.1
BMI (mean kg/m^2)	29.7	29.9
Body weight (mean kg)	90.0	91.8
Health risks [n(%)]		
Tobacco[a]	20 (47.6)	25 (59.5)
Alcohol use	27 (64.3)	27 (64.3)
Benzodiazepine use	6 (14.3)	2 (4.8)
Opiate use	2 (4.8)	2 (4.8)
Co-morbidities [n(%)]		
Past MI	15 (35.7)	11 (26.2)
Past CVA	6 (14.3)	3 (7.1)
Diabetes mellitus	22 (52.4)	20 (47.6)
Hypertension	37 (88.1)	32 (76.2)
Hyperlipidaemia	36 (85.7)	35 (83.3)
Congestive heart failure	3 (7.1)	5 (11.9)
Cancer	6 (14.3)	8 (19.0)
Chronic kidney disease	6 (14.3)	4 (9.5)

There were no statistically significant differences between the dexmedetomidine and propofol groups in any of the characteristics shown

BMI body mass index, *CPB* cardiopulmonary bypass, *CVA* cerebrovascular accident, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction

[a] Tobacco use defined as past or current smoker

extubation in the CABG surgery population [6, 8]. However, these effects have not been conclusively demonstrated. This study investigated the clinical and economic implications of substituting dexmedetomidine for propofol in the elective CABG surgery population. The results of this study indicate that dexmedetomidine patients had a significantly shorter duration of mechanical ventilation, when analysed as a continuous variable (i.e. difference in means) as well as a categorical variable (i.e. extubation within 6 h). ICU LOS and total post-operative hospital LOS were significantly lower for the dexmedetomidine group only when analysed categorically (i.e. ICU LOS $\leq$48 h, total post-operative LOS $\leq$5 days). These variables were not statistically significant when examined continuously, perhaps somewhat attributable to the large variability observed in these measures as well as our limited sample size. Multivariable analysis to control for relevant covariates indicates that, not surprisingly, experiencing a post-operative medical complication is the most significant predictor of increased post-operative LOS. Choosing dexmedetomidine was also significant, and results in decreased post-operative LOS. Renal function also contributes to post-operative LOS, though non-significant, with a trend towards higher serum creatinine resulting in a longer stay. Though only ten patients (six dexmedetomidine, four propofol) in the study had a history of chronic kidney disease, we posit that some of these individuals may have required dialysis, resulting in prolonged hospitalisation.

Several studies have been published comparing the use of propofol and dexmedetomidine in the cardiac surgery population [8, 10, 15–17]. These studies reported no significant difference in duration of mechanical ventilation, but numerical differences favoured patients sedated with dexmedetomidine, as was seen in our study. When dexmedetomidine was added as adjunctive therapy to sedation with midazolam and propofol, a retrospective outcomes analysis revealed significant cost savings with a significantly decreased duration of mechanical ventilation [9]. In terms of additional drug therapy, one randomised, open-label study demonstrated significant decreases in adjunctive therapy such as analgesics, antiemetics, β-blockers and diuretics with dexmedetomidine [8]. With respect to adjunctive opioid consumption, the remaining studies vary greatly [16–18]. These variations may be attributed to differences in study design and patient selection.

Unfortunately, drug shortages have become all too commonplace throughout the US, and necessitate careful response from healthcare providers in determining how to allocate residual supplies of the scarce drug based on medical need and appropriateness, while at the same time implementing an interchange programme for patients for whom an alternative agent is acceptable. This requires

Table 2 Clinical outcomes of coronary artery bypass graft patients sedated on dexmedetomidine versus propofol in the matched cohorts ($n = 84$)

	Dexmedetomidine ($n = 42$)	Propofol ($n = 42$)	Significance (p value)
Outcomes			
Continuous measures			
Duration of mechanical ventilation [mean hours (SD)]	11.8 (22.3)	22.6 (39.9)	<0.01*
Post-operative ICU LOS [mean days (SD)]	2.3 (2.5)	3.3 (3.3)	0.055
Post-operative total hospital LOS [mean days (SD)]	6 (2.5)	7.5 (4.0)	0.062
Categorical measures			
Duration of mechanical ventilation ≤6 h [*n* (%)]	24 (57.1)	7 (16.7)	0.0001*
Post-operative ICU LOS ≤48 h [*n* (%)]	34 (81.0)	24 (57.1)	0.018*
Post-operative hospital LOS ≤5 days [*n* (%)]	25 (59.5)	16 (38.0)	0.049*
Post-operative medical complications			
Stroke [*n* (%)]	1 (2.4)	2 (4.8)	0.542
Atrial fibrillation [*n* (%)]	14 (33.3)	18 (42.9)	0.369
Acute renal failure [*n* (%)]	3 (7.1)	2 (4.8)	0.665
Prolonged mechanical ventilation [*n* (%)]	4 (9.5)	9 (21.4)	0.131
Mediastinal infection [*n* (%)]	1 (2.4)	2 (4.8)	0.557
Myocardial infarction [*n* (%)]	0 (0)	1 (2.4)	0.314
Re-operation following initial procedure [*n* (%)]	2 (4.8)	0 (0)	0.152
Any post-operative complication [*n* (%)][b]	22 (52.4)	23 (54.8)	0.827
Complications per patient [mean (SD)]	0.60 (0.828)	0.81 (0.773)	0.224
Sedation drug therapy			
Sedation drug dose [mean (SD)]	398 μg (518)	2,613 mg (4,480)	–[a]
Midazolam dose equivalent [mean (SD)]	1.1 mg (4.8)	0.1 mg (0.3)	0.008*
Fentanyl dose equivalent [mean (SD)]	320 μg (988)	699 μg (893)	0.538
Adverse events related to sedation drug therapy			
Hypotension [*n* (%)][c]	21 (50.0)	23 (54.8)	0.662
Bradycardia [*n* (%)][d]	3 (7.1)	1 (2.4)	0.306

SD standard deviation, *ICU* intensive care unit, *LOS* length of stay

* Denotes statistically significant differences

[a] Significance testing for mean dose of sedation drug therapy not performed since dexmedetomidine and propofol are dosed differently

[b] Any complication defined as having ≥1 of the complications shown

[c] Hypotension adverse event defined as mean arterial pressure <65 mmHg during sedation therapy

[d] Bradycardia adverse event defined as heart rate <60 beats per minute during sedation therapy

coordination on multiple levels and typically involves pharmacy purchasing staff, pharmacy leadership, clinical pharmacists, medical staff and nursing staff. The cost of coordinating these personnel and resources were outside the scope of our study, but one prior study estimated additional annual labour costs of about US$50,000 associated with drug shortage management in larger hospitals such as our facility [19].

It would be useful if healthcare providers could anticipate potential drug shortages. One recent tactic that may be beneficial is Executive Order 13588, signed by President Obama to broaden the reporting of discontinued pharmaceutical manufacturing, expedite regulatory review of drug alternatives and review the behaviours of market participants (such as stockpiling and price gouging) [20, 21]. Coincidentally, the US Senate and House of Representatives both drafted legislative bills with similar objectives regarding drug shortages [18]. Both pieces of legislation include language to amend the definition of drug shortages; mandate early notification by manufacturers to the FDA of any potential shortage; and broaden the authority of the FDA to establish civil penalties, expedite inspection procedures and disseminate the latest information on current shortages. One tactic that the FDA has employed is publication of shortages on a continuously updated website [10]. However, despite these efforts, minimising shortages and their impact will remain challenging, since they stem from a variety of manufacturing

Table 3 Predictors of post-operative length of stay based on multivariate model ($n = 84$)

	Standardised coefficient (beta)[a]	Significance	95 % CI
Constant	–	0.000	3.126, 8.096
Either current or past smoker	−0.153	0.135	−2.417, 0.333
Number of co-morbidities	0.043	0.685	−0.390, 0.591
Renal function (serum creatinine level)	0.191	0.074	−0.042, 0.908
Post-operative medical complication[b]	0.289	0.008*	−0.532, 3.391
Sedation drug dexmedetomidine	−0.212	0.047*	−2.854, 0.020
Hypotension adverse event[c]	0.103	0.315	−0.679, 2.080
Bradycardia adverse event[d]	0.110	0.286	−1.495, 4.994

Results from a backwards elimination model with R-squared 0.266 are shown which included the following variables: age, male gender, number of co-morbidities, current or past smoker, current or past alcohol use, current or past opiate use, current or past benzodiazepine use, body mass index, renal function (serum creatinine level), number of diseased cardiac vessels, sedation drug was dexmedetomidine, hypotension adverse event resulting from sedation, bradycardia adverse event resulting from sedation; post-operative medical complication

LOS length of stay

* Denotes statistically significant predictors of post-operative LOS

[a] Standardised coefficients indicate impact of variables shown on post-operative LOS

[b] Post-operative medical complication refers to having ≥1 of the following: stroke, acute renal failure, prolonged mechanical ventilation, mediastinal infection, atrial fibrillation, myocardial infarction, re-operation following initial procedure

[c] Hypotension adverse event defined as mean arterial pressure <65 mmHg during sedation therapy

[d] Bradycardia adverse event defined as heart rate <60 beats per minute during sedation therapy

Table 4 Hospital costs of coronary artery bypass graft patients sedated on dexmedetomidine versus propofol matched patient cohorts (all values in US$, year 2012 values; $n = 84$)

	Dexmedetomidine [mean per patient (SD)] ($n = 42$)	Propofol [mean per patient (SD)] ($n = 42$)	Difference in means[a]
Sedation drug therapy	146 (190)	30 (51)	116
Post-operative ICU room and board	4,494 (4,995)	6,495 (6,627)	−2,001
Post-ICU telemetry room and board	5,617 (2,129)	6,364 (4,537)	−747
Total post-operative room and board	10,111 (4,915)	12,859 (7,194)	−2,748
Net financial benefit[b]	–	–	−2,632

ICU intensive care unit, *SD* standard deviation

[a] Negative values indicate cost savings

[b] Net financial benefit calculated as sum of differences in mean post-operative ICU costs and mean post-ICU telemetry room and board less the mean cost of sedation drug therapy

issues and entail complex economic, legal, regulatory, policy and clinical issues.

We acknowledge that our study has several important limitations. The primary limitation is that it was a retrospective chart review conducted at a single institution. Furthermore, since we included two different cohorts of patients in two different timeframes, changes in clinical staff and leadership during the study timeframe may influence our results. We attempted to ensure comparability by patient matching, but during the two time periods, there were different nurses, physicians and surgeons responsible for the care of these patients. Another major limitation of this study was the small sample size and that it included only isolated, elective CABG patients, so the results may not be applicable to other cardiothoracic populations. However, further studies are warranted to investigate the clinical and economic benefit of dexmedetomidine in other cardiac surgery patients. Since dexmedetomidine may itself exert cardioprotective effects, the clinical and economic benefit associated with this drug may be best elucidated in other (i.e. non-CABG) cardiac surgery patients, especially those anticipated to have shorter intubation times [6, 8].

Another limitation is that we did not document the number and doses of vasopressors or inotropes used, which

could impact the incidence of hypotension and bradycardia in both groups. An increased requirement for vasopressors or inotropes would contribute to higher drug costs and could translate to a greater incidence of adverse events, which would potentially prolong LOS. Finally, in terms of our cost measures, this pharmacoeconomic analysis only accounted for cost of drug therapy and average hospital room and board and did not capture billing information and any ancillary costs, such as cost of personnel, laboratory testing and mechanical ventilation. We limited our analysis to room and board and drug costs because they are most relevant to decision makers at our institution.

Despite these limitations, our study has several advantages. First, our analysis reports on the institutional impact of a drug shortage, whereas prior studies present only clinical findings. Also, our study was performed in a large, urban, tertiary care university hospital, thus providing benchmark utilisation values for other similar institutions. Since we had access to both clinical outcome data and institution-specific cost data, our findings are based on real-world outcomes in a patient care setting. Finally, the cohorts were statistically well-matched, strengthening the results of this comparison.

5 Conclusion

The results of this study support the use of dexmedetomidine as an alternative to propofol in CABG patients receiving mechanical ventilation. Along with an increase in achieving duration of mechanical ventilation $\leq$6 h, decreased LOS in the ICU resulted in significant cost savings to our institution by directly saving on room and board costs. We estimated considerable patient cost savings resulting from the interchange, approximating more than US$2,600 per patient in our study population. Additional savings may be derived from preventing post-operative medical complications that result in a longer duration of mechanical ventilation or prolonged care in the ICU or post-ICU wards.

This work, and the work of other institutions, is necessary to better understand the implications of drug shortages. Intuitively, drug shortages may be assumed to negatively impact clinical and economic outcomes. However, our findings refute this notion. Further pharmacoeconomic studies are warranted and should be directed towards other cardiothoracic surgical or critically ill populations to determine the cost benefit of substituting dexmedetomidine in these patients.

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Dr. McDaniel conceived the idea and contributed to the overall design of the project and manuscript review.

Dr. Pizzi performed all data analysis and participated in manuscript revisions.

Dr. Thoma contributed to the overall protocol development, performed data collection, manuscript edits, and will act as the overall guarantor.

Dr. Wordell contributed to the overall design of the project and manuscript review.

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