The Perioperative Use of Dexmedetomidine in Pediatric Patients with Congenital Heart Disease: An Analysis from the Congenital Cardiac Anesthesia Society-Society of Thoracic Surgeons Congenital Heart Disease Database

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BACKGROUND: Dexmedetomidine is a selective α2 receptor agonist with a sedative and cardio-pulmonary profile that makes it an attractive anesthetic for pediatric patients with congenital heart disease (CHD). Although several smaller, single-center studies suggest that dexmedetomidine use is gaining traction in the perioperative setting in children with CHD, there are limited multicenter data, with little understanding of the variation in use across age ranges, procedural complexity, and centers. The aim of this study was to use the Congenital Cardiac Anesthesia Society-Society of Thoracic Surgeons (CCAS-STS) registry to describe patient- and center-level variability in the use of dexmedetomidine in the perioperative setting in children with heart disease.

METHODS: To describe the use of dexmedetomidine in patients for CHD surgery, we analyzed all index cardiopulmonary bypass operations entered in the CCAS-STS database from 2010 to 2013. Patient and operative characteristics were compared between those who received intraoperative dexmedetomidine and those who did not. Selective outcomes associated with dexmedetomidine use were also described.

RESULTS: Of the 12,142 operations studied, 3600 (29.6%) received perioperative dexmedetomidine (DEX) and 8542 did not receive the drug (NoDEX). Patient characteristics were different between the two groups with the DEX group generally exhibiting both lower patient and procedural risk factors. Patients who received dexmedetomidine were more likely to have a lower level of Society of Thoracic Surgeons mortality complexity than patient who did not receive it. Consistent with their overall lower risk profile, children in the DEX group also demonstrated improved outcomes compared with patients who did not receive dexmedetomidine.

CONCLUSIONS: We described the growing use of dexmedetomidine in children anesthetized for surgical repair of CHD. Dexmedetomidine appears to be preferentially given to older and larger children who are undergoing less complex CHD surgery. We believe that the data provided in this study are the largest investigating the use of an anesthetic drug in CHD patients. It is also the first analysis of the anesthesia data in the CCAS-STS Congenital Heart Disease database.

(Anesth Analg 2016;XXX:00–00)

Dexmedetomidine is a selective α2 adrenergic receptor agonist that may be administered orally, intranasally, or intravenously and is now indicated for use both in critical care and perioperative settings. The drug’s sedative effect is via binding to α2 receptors in the locus ceruleus of the brain, leading to decreased noradrenergic output and increased γ-aminobutyric acid firing.1 Dexmedetomidine has become an increasingly popular agent in pediatric anesthesia because of its ability to promote a natural, non-Rapid Eye Movement sleep while maintaining airway patency and breathing.2 It is recognized that dexmedetomidine has potential adverse cardiovascular side effects, including bradycardia, hypotension, and hypertension; however, it is generally felt that these effects are self-limiting and typically are clinically insignificant.3–7 The sedative effects and cardiopulmonary profile of the drug make it an attractive anesthetic adjuvant for pediatric patients with congenital heart disease (CHD). Dexmedetomidine has been used for preoperative sedation and anxiolysis, cardiac and noncardiac procedural sedation, sedation in the intensive care unit (ICU), antiarrhythmia therapy, treatment of postoperative delirium, and as part of the intraoperative anesthetic management during CHD surgical repairs.8

There are data to suggest that the perioperative use of dexmedetomidine improves morbidity and mortality in adult patients undergoing cardiac surgery.9 Although
several smaller, single-center studies suggest that dexmedetomidine use is gaining traction in the perioperative setting in children with CHD, there are limited multicenter data, with little understanding of the variation in use across age ranges, procedural complexity, and centers. Starting in 2010, the Congenital Cardiac Anesthesia Society (CCAS) and the Society of Thoracic Surgeons (STS) joined together to create the CCAS-STS database. Before this, there were no prospective multicenter registries specifically geared toward the highly specialized field of congenital cardiac anesthesia. The aim of this study was to use the CCAS-STS registry to describe patient- and center-level variability in the use of dexmedetomidine in the perioperative setting in children with heart disease. We also examined the association of dexmedetomidine with outcomes in children undergoing surgical repair of CHD. To our knowledge, this is the first time the CCAS-STS database has been used to answer questions pertaining to the anesthetic management of children with CHD undergoing surgical repair. It is also the largest patient population of children with cardiac disease studied to describe the usage of a particular anesthetic agent.

METHODS
The STS database was established in 1989 as an initiative for quality improvement and patient safety among cardiothoracic surgeons. In 1994, the STS database added a component for congenital heart surgery, the Congenital Heart Surgery Database (STS-CHSD). The CCAS was formalized in 2005 and immediately began working with the STS-CHSD to include anesthesia-related information in their data set. The STS-CHSD version 3.0, which became effective in January 2010, was the first version to incorporate anesthesia data. The CCAS-STS database along with the STS-CHSD is updated on a triennial basis to accommodate changes in procedures, diagnoses, monitoring modalities, medications, and adverse events.

To describe the use of dexmedetomidine in patients for CHD surgery, we analyzed all index cardio pulmonary bypass operations entered in the CCAS-STS database from 2010 to 2013 (data version 3.0). The total number of eligible operations during this interval was 23,011 (37 centers).

Exclusion criteria were then applied, including isolated patent ductus arteriosus closure in infants ≤2.5 kg or organ procurement surgery (n = 4), patients ≥18 years of age (n = 2279), and patients with missing anesthetic use of primary, intraoperative, or transfer medications (n = 2279). For analytic purposes, we also excluded all patients with missing STS-European Association for Cardio-Thoracic Surgery (EACTS) Society of Thoracic Surgeons (STAT) Mortality Score (n = 496). The STS-EACTS STAT Mortality Score was developed as a tool for grouping procedures with a similar empirically estimated risk of in-hospital mortality. The score facilitates analyses across the wide spectrum of distinct congenital heart surgery operations and across various institutions. Finally, to ensure high-quality data and to maintain consistency with previous STS-CHSD analyses, we excluded participating centers with anesthesia data missing for >15% (n = 7 centers, 6234 patients). The remaining observations for analysis totaled 12,142, from 29 centers in the United States (out of an estimated 122 centers performing congenital heart surgery).

Patients were considered to have been treated with dexmedetomidine if they received the drug intraoperatively (primary maintenance agent or intraoperative medication) and/or postoperatively at the time of transfer to the ICU/postanesthesia care unit. Patients who were started on dexmedetomidine after arrival to the ICU were not included in the treatment group. The baseline characteristics of patients in the study population being analyzed who received dexmedetomidine were compared with those who did not receive the medication. No attempt to control for drug dosage or duration of administration was made, because these data are not collected. Patient characteristics compared included age group (neonates/infants/children), age at surgery, sex, race, weight and height at surgery, weight-for-age Z-score, STAT-EACTS complexity, prematurity, presence of any other preoperative risk factors except mechanical ventilation to treat cardiorespiratory failure, presence of syndromes/noncardiac anatomic abnormalities/chromosomal abnormalities, preoperative mechanical ventilation to treat cardiorespiratory failure, number of prior cardiothoracic operations, and number of prior cardiopulmonary bypass cardiothoracic operations. The operative characteristics examined included primary diagnosis, primary procedure, cardiopulmonary bypass time, aortic cross-clamp time, circulatory arrest time, total time of tracheal intubation, postoperative tracheal intubation time, STS-EACTS STAT mortality level, and the presence of single ventricle as the primary diagnosis.

The primary outcomes examined with the association of dexmedetomidine administration were in-hospital mortality and the presence of any complications. Secondary outcomes were postoperative length of stay, any major complication (defined previously as renal failure, neurologic deficit, arrhythmia necessitating pacemaker, postoperative mechanical circulatory support, and unplanned reoperation), arrhythmia, postoperative neurologic deficit, and duration of mechanical ventilation.

Statistical Methods
Study population characteristics were described overall and stratified by procedural cohort using standard summary statistics including counts (percentages) for categorical variables and median (interquartile range) for continuous variables. Standard hypothesis tests including 2 tests were used to compare the distribution of categorical and continuous variables between different groups. All analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC). A P value <0.05 was considered statistically significant; 95% confidence interval of median for continuous variable was attained using distribution-free confidence limits for percentiles, and 95% confidence interval of % for binary variable were attained using asymptotic Wald confidence limits for binomial proportion.

RESULTS
Of the 12,142 operations studied, 3600 (29.6%) received perioperative dexmedetomidine (DEX) and 8542 did not receive...
Patients treated with dexmedetomidine were found to have shorter aortic cross-clamp times and shorter circulatory arrest times than those children not treated with the drug, likely reflecting the differences in procedural complexity.

Consistent with their overall lower risk profile, children in the DEX group also demonstrated improved outcomes. Patients receiving dexmedetomidine had an in-house mortality rate of 1.33% compared with a 4.11% mortality rate in the NoDEX group, \( P < 0.0001 \). Patients in the DEX group had a lower percentage of any complications and major complications in comparison with those in the NoDEX group (30.1% vs 44.6%, 7.8% vs 14.0%, respectively). Dexmedetomidine use was associated with a lower incidence of arrhythmia and postoperative neurologic injury (12.7% vs 20.8, 1.3% vs 2.7%, respectively), a shorter duration of mechanical ventilation (median 6.0 vs 23.5 hours) and a shorter length of stay (median 6.0 vs 7.0 days). All the results mentioned here carried a \( P \) value of <0.0001.

Patients’ operative characteristics were also different between the DEX and NoDEX groups (Table 2). Specifically, patients who received dexmedetomidine were more likely to have a lower level of STAT mortality complexity than patients who did not receive the drug. Thus, patients in the DEX group generally underwent surgeries of lower complexity and lower mortality risk. However, 18.5% of the patients in each group carried a single-ventricle primary diagnosis. Patients treated with dexmedetomidine were...
Dexmedetomidine Use in the CCAS-STS Database

Table 3. Descriptive Outcomes of Children Undergoing Repair of Congenital Heart Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall, n = 12,142 (%)</th>
<th>No DEX, n = 8542 (%)</th>
<th>Yes DEX, n = 3600 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>Yes 399 (3.3, 3.0–3.6)</td>
<td>351 (4.1, 3.7–4.6)</td>
<td>48 (1.3, 1.0–1.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any complication</td>
<td>Yes 4894 (40.3, 39.4–41.2)</td>
<td>3811 (44.6, 43.6–45.7)</td>
<td>1083 (30.1, 28.6–31.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any major complication</td>
<td>Yes 1474 (12.1, 11.6–12.7)</td>
<td>1193 (14.0, 13.2–14.7)</td>
<td>281 (7.8, 6.9–8.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Yes 2236 (18.4, 17.7–19.1)</td>
<td>1779 (20.8, 20.0–21.7)</td>
<td>457 (12.7, 11.6–13.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative</td>
<td>Yes 277 (2.3, 2.0–2.6)</td>
<td>231 (2.7, 2.4–3.0)</td>
<td>46 (1.3, 0.9–1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neurologic deficit</td>
<td>Median, 95% CI (h)</td>
<td>16.0, 15.3–16.7</td>
<td>23.5, 22.8–24.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of mechanical</td>
<td>Median, 95% CI (d)</td>
<td>6.0, 6.0–6.0</td>
<td>7.0, 7–7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ventilation</td>
<td>Patient LOS</td>
<td>6.0, 6.0–6.0</td>
<td>6.0, 5.0–6.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

95% CIs of median for continuous variable were attained using distribution-free confidence limits for percentiles.18 95% CIs of % for binary variable were attained using asymptotic Wald confidence limits for binomial proportion.17

CI = confidence interval; LOS = length of stay.

Table 4. Use of Dexmedetomidine by Surgery Year

<table>
<thead>
<tr>
<th>Dexmedetomidine usage</th>
<th>2010, n (%)</th>
<th>2011, n (%)</th>
<th>2012, n (%)</th>
<th>2013, n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1676 (73.3)</td>
<td>2567 (78.3)</td>
<td>2188 (70.9)</td>
<td>2111 (60.5)</td>
<td>8542</td>
</tr>
<tr>
<td>Yes</td>
<td>612 (26.7)</td>
<td>711 (21.7)</td>
<td>897 (29.1)</td>
<td>1380 (39.5)</td>
<td>3600</td>
</tr>
<tr>
<td></td>
<td>2288</td>
<td>3278</td>
<td>3085</td>
<td>3491</td>
<td>12,142</td>
</tr>
</tbody>
</table>

Shows that the total number of surgical cases using dexmedetomidine increased in each year of the study, and the percentage of dexmedetomidine usage increased from 2011 to 2013.

DISCUSSION

CHD is one of the most common anomalies at birth, with an incidence of 4 to 8 per 1000 births.18 Advances in surgical, anesthetic, and ICU management have greatly improved outcomes. However, CHD is still implicated in 30% to 50% of infant mortality because of congenital anomalies.19 Importantly, CHD is a significant risk factor for anesthesia-related cardiac arrests.20 Many more patients suffer morbidities, such as arrhythmia requiring a pacemaker, neurologic deficits, renal injury, prolonged mechanical ventilation, mechanical circulatory support, and reoperation. Developing new medications and techniques to reduce these risks remains a priority in the perioperative care of this patient population. During the last several years, dexmedetomidine has found an increasing role in the perioperative management of children with CHD, as familiarity with its potential benefits and side effects become better known.

A number of published studies describe the clinical use of dexmedetomidine in pediatric congenital heart patients during surgical repair and in the cardiac ICU. The medication is effective and well tolerated in these patients.4–7 Patients receiving dexmedetomidine have been observed to require less opioid and benzodiazepine medications.6,7 Treatment with dexmedetomidine in associated with deeper levels of sedation and a decreased time to extubation.3 Patients receiving dexmedetomidine have also demonstrated an attenuated hemodynamic and neuroendocrine response to surgery and cardiopulmonary bypass.21,22 The drug has also been used for its antiarrhythmic properties.23,24 In addition, a number of animal studies are beginning to examine the role of dexmedetomidine in inhibiting inflammation, attenuating ischemic-reperfusion injury, and potentially providing neuroprotection during anesthesia.25–31

Despite the growing number of clinical studies, these generally involve small sample sizes and do not report on the clinical outcomes of this patient population. A study by Fuhai et al.9 involved a much larger subject group and reported that mortality and major morbidity are improved in adult patients undergoing cardiac surgery who receive dexmedetomidine. However, the adult cardiac population is physiologically very different from the pediatric patients with CHD. Thus, this very good study cannot be extrapolated to children. Furthermore, though there are a number of animal studies that suggest that dexmedetomidine may serve a protective role in the inflammatory and ischemic-reperfusion injury pathways that occur with bypass, it is too soon to translate these experiments to the bedside and patient outcome.

Our study is unique in that it represents the first time a group of anesthesia patients was analyzed from the CCAS-STS—Congenital Heart Disease Database. The >12,000 patients, from 29 medical centers, represent a uniquely large sample size for a study examining the use of a specific medication in the anesthetic management of children with CHD. Our data show that dexmedetomidine is used in a large percentage of children undergoing cardiopulmonary bypass for surgical repair of CHD, with 30% of our patient population treated with dexmedetomidine. The data also demonstrate that dexmedetomidine use increased during the time period of our study. Consistent with their lower risk, patients in the DEX group had lower mortality and major morbidity rates in comparison with the NoDEX group. In addition, patients treated with dexmedetomidine were less likely to...
experience complications after surgery. They were separated from mechanical ventilation and extubated sooner, although we do not know whether they were extubated while still receiving the medication. The DEX patients spent less time in the hospital than patients who did not receive dexmedetomidine.

However, the pediatric congenital heart patient population is a very heterogeneous group, with widely variable expected outcomes because of differences in the severity of the defect, the age at which the patient is operated on, and the likelihood of other comorbidities such as preexisting neurologic injury. Analysis of the data demonstrates that dexmedetomidine was preferentially given to older and larger patients. There also seems to be a preference in using the drug in patients who were at less risk of suffering a perioperative death, based on the lower STAT mortality level in the DEX group. The DEX patients seemed to undergo less complex surgery, as reflected in their procedural complexity scores, as well as their lower aortic cross-clamp times and circulatory arrest times.

Figure 1. Variation of dexmedetomidine use across all sites among overall cohort.

Figure 2. Each center’s percent usage of dexmedetomidine across surgery year among overall cohort. The graph represents each program. No trend can be reached using this graph.
Although one of the original objectives of this study was to evaluate the impact of dexmedetomidine use on outcomes, including perioperative mortality, major morbidity, and propensity for arrhythmia, our initial exploratory analysis demonstrated that patients receiving DEX underwent lower complexity procedures and had a lower risk of mortality. Despite several attempts, we were unable to appropriately balance the groups for a meaningful multivariable analysis; there were simply too many unknowns regarding the patient-, provider-, and center-level factors that contribute to dexmedetomidine use.

There are inherent limitations in using a large database to answer clinical questions such as ours. First, all such research is retrospective in design. Second, the CCAS-STS database is voluntary and is not a random sample of pediatric hospitals. In addition, we were unable to consider dose or duration of drug administration in our analysis, because this information is not captured in the database. We also did not have the capability to analyze the data based on different surgeons. Although the STS conducts random audits of their surgical participants annually, the CCAS currently lacks audit or data verification for the anesthesia component of the registry. For the timeframe analyzed in this cohort, the CCAS-STS registry was in its infancy. As with any new registry, there is a learning curve for centers as they develop the resources needed to ensure high-quality data submission. For these reasons, we excluded centers with high levels of missing data (n = 8) as well as patients with missing data for key variables. In total, nearly half of the records in the registry were ineligible for inclusion in the analysis. Although exclusions are standard practice for any registry-based analysis, this does introduce the possibility of some bias when generalizing these data to the broader spectrum of centers performing cardiac anesthesia. As the CCAS-STS database matures, data quality would be expected to improve, and future analyses may provide a broader perspective.

Finally, pediatric cardiac surgery patients cover a wide range of age and size and undergo many different types of surgery with a wide range of illness severity and surgical complexity. When looking at outcomes, a first glance appears to suggest an improvement in mortality and morbidities in the DEX group. However, because of the differences in patient and surgical characteristics in each study group, and our inability to statistically adjust for confounding variables, we are unable to conclude that dexmedetomidine provides any improved outcomes for pediatric CHD patients having cardiopulmonary bypass surgery.

CONCLUSIONS

Despite the limitations of this study, we are able to describe the growing use of dexmedetomidine in children anesthetized for surgical repair of CHD. For the time epoch in our study, dexmedetomidine appears to be preferentially given to older and larger children who are undergoing less complex CHD surgery. Although the use of dexmedetomidine in the anesthetic management of CHD surgery has been increasing annually, there is wide center variability in use, and the drug has not been adopted by all anesthesiologists who care for these patients. Furthermore, there appears to be some reluctance to give dexmedetomidine to younger, smaller patients who are facing more complex surgery and are at a higher risk of death. Although we did not investigate the reasons for this discrepancy, one can conjecture that, with growing knowledge and experience, dexmedetomidine may find its way into an expanding patient population. We believe that this study is the largest investigating the use of an anesthetic drug in CHD patients. It is also the first analysis of the anesthesia data in the CCAS-STS Congenital Heart Disease Database. This registry continues to expand by tens of thousands of patients annually. Perhaps with continued growth, a larger population in the data set will allow future analyses to comment on outcomes associated with dexmedetomidine use with greater confidence and potential subgroup analysis in types of surgery, such as repair of Tetralogy of Fallot, which are associated with specific adverse events, such as postoperative arrhythmias, for which dexmedetomidine may be particularly useful.

DISCLOSURES

Name: Lawrence I. Schwartz, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Lawrence I. Schwartz has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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Attestation: Mark Twite has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Attestation: Sunghee Kim has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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