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Use of vasoactive agents in postoperative pediatric cardiac patients: Insights from a national database

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Abstract

Objective: The main goal of this study is to examine the variation in vasoactive agent prescription patterns across a large cohort of patients. In addition, we sought to determine the association between the number of vasoactive agents used during admissions and characteristics of admissions utilizing varying numbers of vasoactive agents.

Methods: This was a multi-institutional, cross-sectional study of the pediatric health information system database of patients who underwent congenital heart surgery and received vasoactive agents from 2004 to 2015. The international classification of disease-9 (ICD-9) codes were used to select admissions to those only pertaining to cardiac patients. The vasoactive agents investigated included epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and vasopressin.

Results: A total of 43 441 postoperative pediatric cardiac admissions were identified and included in the final analyses. Of these, a majority used at least one vasoactive agent at some point during the admissions with the median being three vasoactives. Each vasoactive was utilized with decreasing frequency throughout the study period except for vasopressin which increased in frequency of use. After adjusting for multiple confounding factors, only milrinone was associated with decreased inpatient mortality in any postoperative subset, while the rest of the vasoactive were associated with increased inpatient mortality in some of the postoperative subsets.

Conclusion: Vasoactive agents have decreased in frequency of use in postoperative pediatric cardiac admissions, except for vasopressin. Only milrinone was found to be associated with decreased inpatient mortality in any subset of these patients, while all other vasoactive agents were found to be associated with increased inpatient mortality at least in one of the subsets.

KEYWORDS

epinephrine, inoptrope, milrinone, vasopressin, vasoconstrictor

1 | INTRODUCTION

Vasoactive agents are one of the most frequently used tools in the management of patients after congenital heart surgery.[1] These agents are commonly initiated in the operating room at the discretion of the caring team. Some of the considerations typically accounted for the selection of these agents are patient age, postoperative echocardiography findings and vital signs status among others. However, practice variation exists in the selection, timing of initiation, and the number of these agents required for a particular congenital lesion or type of surgery.[2]

Due to the association between practice variation and increase in cost, hospital length of stay, and potential adverse outcomes, we decided to carry out the following study.[3-5] The main goal of this

study is to examine the variation in vasoactive agent prescription patterns across a large cohort of patients. In addition, we sought to determine the association between the number of vasoactive agents used during admissions and characteristics of admissions utilizing varying numbers of vasoactive agents.

2 | METHODS

The institutional review board at Texas Children's Hospital approved this study. Consent from individual patients was not obtained by the authors of this study as this study utilized de-identified data from a national database. The study is in compliance with the Helsinki declaration.

2.1 | Pediatric health information system database

Data for this study were obtained from the pediatric health information system. This is an administrative and billing database that contains inpatient, emergency department, ambulatory surgery, and observation data from not-for-profit, tertiary care pediatric hospitals in the United States. The 53 hospitals that contribute data to pediatric health information system database are affiliated with the Children's Hospital Association (Lenexa, KS), a business alliance of children's hospitals. Six of those 53 hospitals also submit laboratory and radiology data to PHIS+. Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, procedures, and charges. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database.

2.2 | Patient identification

Admissions from 2004 to 2015 in the pediatric health information system database were utilized for this study. Table 1 outlines the cardiac diagnoses, and the corresponding international classification of disease-9 (ICD-9) codes that were used to initially filter admissions to those only pertaining to cardiac patients. After this, group of patients was identified then those with cardiac surgery were identified using ICD-9 procedure codes outlined in Table 1. Admissions with cardiac surgery were then looked at further to identify only those that had a postoperative length of 0 days to ensure that all interventions in the critical care setting were postoperative. Ultimately, it was these postoperative cardiac surgical admissions that were included in the final analyses. Admissions that did not include cardiac surgery and had a preoperative length of stay greater than 0 were excluded. Any reference to "admission" for the remainder of this manuscript will refer to the admissions meeting the aforementioned inclusion criteria unless otherwise specified.

Medications utilized during admissions is recorded in the pediatric health information system database. The following inotropes and vasoconstrictors and their use were identified for this study: epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and vasopressin. The use of each individual was marked as being present or absent for each admission.

2.3 | Data collection

Demographic information include age and gender were collected for each admission. Admissions characteristics such as length of stay, billed, charges, and inpatient mortality were also collected. Comorbidities of interest that were captured for this study included: tachyarrhythmia, bradyarrhythmia, heart failure, acute kidney injury, hypothyroidism, pulmonary hypertension, and syndromes.

2.4 | Statistical analyses

A cross-sectional study was conducted. Continuous variables are reported using median and range, while categorical variables are reported using absolute frequency and percentages. Continuous variables were analyzed using a Mann-Whitney *U* test, while categorical variables were analyzed using Fisher's exact test due to the nonnormal distribution of the data.

The initial analysis consisted of simply characterizing the cohort of admissions deemed appropriate for inclusion. The frequency of admissions with each specific vasoactive agent by year was then calculated. Age at admission, RACHS score of surgery, length of stay, and billed charges were then compared by absolute number of vasoactive agents utilized during the admission.

Next, regression analyses were conducted to determine the impact of each specific vasoactive agent on admission characteristics. Linear regressions were conducted for length of admission and billed charges as both of these variables were continuous variables. Two separate linear regressions were conducted, one with length of admission as the dependent variable and the other with billed charges as the dependent variable. In both of these regression analyses all congenital heart malformations, previously mentioned comorbidities, and each vasoactive agent were included as independent variables. A logistic regression was conducted with inpatient mortality as the dependent variable. Independent variables entered into the regression were the same as described for the linear regressions.

Next, regression analyses were conducted again but only for admissions with specific cardiac surgeries compared to the prior regressions that were conducted including all postoperative cardiac surgical admissions. Regression analyses were repeated for postoperative admissions after the specific surgeries: complete repair of atrioventricular septal defect, complete repair of tetralogy of Fallot, complete repair of total anomalous pulmonary venous connection, complete repair of common arterial trunk, arterial switch, atrial switch, right ventricle to pulmonary artery conduit placement, Glenn, Fontan, systemic to pulmonary artery shunt placement, and heart transplant.

All statistical analyses were conducted using SPSS version 23.0. A *P* value of less than .05 was considered statistically significant.

TABLE 1 ICD-9 codes utilized in the study

Gender (male)	23.562 (54.2)
Age (years)	0 (0 to 17)
Cardiac lesion	
Primum atrial septal defect	1219 (28)
Secundum atrial septal defect	20.981 (48.3)
Ventricular septal defect	14 147 (32.6)
Double outlet right ventricle	4488 (10.3)
Tetralogy of Fallot	4945 (11.4)
Pulmonary atresia	2109 (4.9)
Atrioventricular septal defect	6848 (15.8)
Transposition	2628 (6.0)
Congenitally corrected transposition	748 (1.7)
Common arterial trunk	856 (2.0)
Ebstein anomaly	748 (1.7)
Hypoplastic left heart syndrome	5317 (12.2)
Functionally univentricular heart other than HLHS	2829 (6.5)
Coarctation of the aorta	1666 (3.8)
Interrupted aortic arch	301 (0.7)
Partial anomalous pulmonary venous connection	1754 (4.0)
Total anomalous pulmonary venous connection	1385 (3.2)
Systemic venous anomaly	1531 (3.5)
Congenital tricuspid stenosis	2655 (6.1)
Congenital mitral stenosis	660 (1.5)
Congenital pulmonary stenosis	2790 (6.4)
Congenital aortic stenosis	647 (1.5)
Congenital subaortic stenosis	1162 (2.7)
Congenital pulmonary artery anomaly	2250 (5.2)
Congenital coronary anomaly	1202 (2.8)
Cardiac surgery	
Valvuloplasty without replacement, unspecified valve	55 (0.1)
Valvuloplasty without replacement, aortic valve	1341 (3.1)
Valvuloplasty without replacement, mitral valve	2352 (5.4)
Valvuloplasty without replacement, pulmonary valve	1974 (4.5)
Valvuloplasty without replacement, tricuspid valve	2866 (6.6)
Replacement, unspecified valve	9 (0.1)
Tissue replacement, aortic valve	515 (1.2)
Mechanical replacement, aortic valve	381 (0.9)
Tissue replacement, mitral valve	51 (0.1)
Mechanical replacement, mitral valve	322 (0.7)
Tissue replacement, pulmonary valve	1564 (3.6)
Mechanical replacement, pulmonary valve	994 (2.3)
Tissue replacement, tricuspid valve	82 (0.2)
Mechanical replacement, tricuspid valve	136 (0.3)
Operation on papillary muscle	97 (0.2)
Operation on chordae tendinae	76 (0.2)
Annuloplasty	732 (1.7)
Infundibulectomy	1094 (2.5)
Enlargement of existing atrial septal defect	1254 (2.9)
Creation of septal defect	1910 (4.4)
Repair of ventricular septal defect with prosthesis	1258 (2.9)
Repair of ventricular septal defect with tissue	4444 (10.2)
Repair of atrioventricular septal defect with tissue	4004 (9.2)
Total repair of tetralogy of Fallot	3594 (8.3)
Total repair of anomalous pulmonary venous connection	1568 (3.6)
Total repair of common arterial trunk	244 (0.6)
Arterial switch	667 (1.5)
Atrial switch	1357 (3.1)
Right ventricle to pulmonary artery conduit	3107 (7.2)
Heart transplant	365 (0.8)
Systemic to pulmonary artery shunt	1934 (4.5)
Glenn	5600 (12.9)
Fontan	6316 (14.5)
Length of stay (days)	6 (1 to 524)
Billed charges (US dollars)	1 21 780
Extracorporeal membrane oxygenation	1196 (2.8)
Inpatient mortality	807 (1.9)
Number of inoconstrictors	3 (0 to 6)

Any difference mentioned to be "significant" is statistically significant unless otherwise specified.

3 | RESULTS

3.1 | Cohort characteristics

A total of 43 441 admissions were included in this study. Of these, 23 562 (52.2%) were male and the median age was under 1 year of age. Cardiac lesions are outlined in Table 2 with the most frequent being secundum atrial septal defect in 20 981 (48.3%). Cardiac surgeries are also outlined Table 2 with the most frequent being Fontan in 6316 (7.2%).

Median length of stay was 6 days with median billed charges of 121 780 US dollars. Of the total cohort, 1196 (2.8%) required extracorporeal membrane oxygenation. A total of 807 (1.9%) of admissions experienced inpatient mortality (Table 2).

3.2 | Vasoactive agent use in the cohort

Epinephrine was used in 31 598 (72.7%) of admissions, norepinephrine in 1421 (3.3%), dopamine in 28 590 (65.8%), dobutamine in 2882 (6.6%), milrinone in 35 373 (81.4%), and vasopressin in 1704 (3.9%).

Epinephrine use did change over the study period. From 2004 to 2009, there was an increase in epinephrine use after which there

TABLE 2 Characteristics of postoperative pediatric cardiac admissions

Gender (male)	23 562 (54.2)
Age (years)	0 (0-17)
Cardiac lesion	
Primum atrial septal defect	1219 (28)
Secundum atrial septal defect	20 981 (48.3)
Ventricular septal defect	14 147 (32.6)
Double outlet right ventricle	4488 (10.3)
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Mechanical replacement, pulmonary valve	994 (2.3)
Tissue replacement, tricuspid valve	82 (0.2)
Mechanical replacement, tricuspid valve	136 (0.3)
Operation on papillary muscle	97 (0.2)
Operation on chordae tendinae	76 (0.2)
Annuloplasty	732 (1.7)
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Heart transplant	365 (0.8)
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Glenn	5600 (12.9)
Fontan	6316 (14.5)
Length of stay (days)	6 (1-524)
Billed charges (US dollars)	1 21 780
Extracorporeal membrane oxygenation	1196 (2.8)
Inpatient mortality	807 (1.9)
Number of inoconstrictors	3 (0-6)

was a decrease through 2015. In 2004, 71.0% of admissions used epinephrine compared to 63.2% in 2015 ($P < .01$) (Table 3)

Norepinephrine use also varied throughout the course of the study period with an overall decrease in frequency from 4.9% in 2004 to 3.3% in 2015 ($P < .01$) (Table 3).

Dopamine use decreased throughout the course of the study period from 77.6% in 2004 to 46.2% in 2015 ($P < .01$) (Table 3).

Milrinone initially increased from 2004 to 2010 and then decreased from 2012 through 2015. In 2004, milrinone was used in 76.4% of admissions compared to 67.8% in 2015 ($P < .01$) (Table 3).

Vasopressin increased throughout the study period with 1.8% of admissions using vasopressin in 2004 compared to 7.1% in 2015 ($P < .01$) (Table 3).

3.3 | Number of vasoactive agents used during admissions and characteristics of admissions utilizing varying numbers of vasoactive agents

The median number of vasoactive agents used during an admission in this cohort was 3. No vasoactive agents were used in 4229 (9.7%) admissions, one was used in 3939 (9.0%) admissions, two were used in 11 145 (25.6%) admissions, three were used in 21 383 (49.2) admissions, four were used in 2541 (5.8%) admissions, five were used in 198 (0.4%) admissions, and six were used in 6 (0.1%) admissions.

TABLE 3 Frequency of use of each studied vasoactive by year

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Epinephrine	71.0	72.4	73.5	75.3	76.6	74.6	76.5	75.1	76.8	75.3	63.4	63.2
Norepinephrine	4.9	2.9	3.5	3.8	2.8	3.0	3.2	2.6	3.4	3.4	3.1	3.3
Dopamine	77.6	77.6	77.4	72.8	69.4	68.5	67.6	67.1	67.5	61.7	47.2	46.2
Dobutamine	19.2	12.5	10.8	8.8	6.5	7.0	6.4	3.8	5.0	1.8	3.0	1.7
Milrinone	76.4	80.7	84.5	83.3	85.3	84.6	85.9	84.6	86.0	84.2	73.2	67.8
Vasopressin	1.8	1.3	1.8	2.5	2.7	3.0	3.4	3.6	3.6	6.7	7.2	7.1

TABLE 4 Characteristics of admissions by number of vasoactive agents by year

	Admit age (years)	RACHS	Length of stay (days)	Billed Charges (USD)	Inpatient mortality (%)
0	1 (0-17)	2 (0-6)	5 (1-524)	91 589	1.4
1	1 (0-17)	2 (0-6)	5 (1-301)	94 098	1.0
2	1 (0-17)	3 (0-6)	6 (1-403)	115 712	0.8
3	0 (0-17)	3 (0-6)	7 (1-482)	136 056	1.7
4	0 (0-17)	3 (0-6)	10 (1-280)	185 864	8.4
5	0 (0-17)	3 (0-6)	10 (1-249)	202 417	22.7
6	1 (0-6)	2 (1-4)	5 (3-9)	168 413	50.0

Admit age by number of vasoactive agents used was similar with the median age either being 1 year of age or 1 year of age in vasoactive agent groups. RACHS scores were also similar between groups with all groups having a median RACHS score of 2 or 3 for the admit surgery. Length of stay increased with number of vasoactive agents used with a median of 5 days in the no vasoactive agent group compared to 10 for admissions utilizing five vasoactive agents. Billed charges also increased with number of vasoactive agents used with a median of $91 589 in the no vasoactive agent group compared to $202 417 for admissions using five vasoactive agents. Inpatient mortality also increased with number of vasoactive agents used with 1.4% in the no vasoactive agents group compared to 22.7% in admissions using five vasoactive agents. Since the number of admissions utilizing six vasoactive agents was so low, they are not mentioned here in the text but data for these admissions are outlined in Table 4.

3.4 | Effect of specific vasoactive agents on admission characteristics, regression analyses

The independent associations of each specific vasoactive agents with increase in total length of stay and billed charges is outlined in Table 5. This is done for all surgical procedures combined and then as subset analyses for the individual surgeries selected for specific analysis.

With respect to inpatient mortality, only milrinone was found to be independently associated with decrease in inpatient mortality in any of the study settings. Milrinone was found to be independently associated with a decrease in inpatient mortality for the entire cohort, for complete repair of total anomalous pulmonary venous connection, and for the Glenn procedure. No other vasoactive agents were found to be associated with decreased inpatient mortality in any postoperative setting.

With respect to inpatient mortality, a few of the vasoactive agents were found to be independently associated with increased inpatient mortality. Epinephrine was found to be independently associated with increased inpatient mortality for the entire cohort and for the Fontan procedure. Norepinephrine was found to be independently associated with increased inpatient mortality for the entire cohort, complete repair of atrioventricular septal defect, complete repair of tetralogy of Fallot, complete repair of total anomalous pulmonary venous connection, arterial switch, atrial switch, right ventricle to pulmonary artery conduit placement, Glenn procedure, Fontan procedure, systemic to pulmonary artery shunt placement, and heart transplant. Dopamine was found to be independently associated with increased inpatient mortality for the entire cohort, total repair of tetralogy of Fallot, total repair of total anomalous pulmonary venous connection, and Glenn procedure. Dobutamine was found to be independently associated with increased inpatient mortality for the entire cohort, complete repair of tetralogy of Fallot, Glenn procedure, and systemic to pulmonary artery shunt placement. Vasopressin was found to be independently associated with increased inpatient mortality for the entire cohort, right ventricle to pulmonary artery conduit placement, Glenn procedure, and systemic to pulmonary artery shunt.

4 | DISCUSSION

This current study characterizes the use of various vasoactive agents throughout the years in the United States at institutions that

TABLE 5 Summary of independent associations of vasoactive use on admission characteristics for the entire cohort and surgical subsets

	Length of stay (days)	Billed charges (US dollars)	Inpatient mortality (OR, 95%CI)
All surgeries			
Epinephrine	−0.08 (*P* = .67)	+12 705 (*P* < .01)	1.80 (1.40-2.31)
Norepinephrine	4.56 (*P* < .01)	+106 918 (*P* < .01)	4.43 (3.55-5.53)
Dopamine	−0.68 (*P* < .01)	+29 972 (*P* < .01)	1.89 (1.54-2.30)
Dobutamine	+3.60 (*P* < .01)	+29 059 (*P* < .01)	1.57 (1.24-1.98)
Milrinone	−0.15 (*P* = .49)	+26 027 (*P* < .01)	0.37 (0.30-0.47)
Vasopressin	−3.53 (*P* < .01)	−63 599 (*P* < .01)	4.65 (3.68-5.86)
Complete repair of atrioventricular septal defect			
Epinephrine	−1.13, (*P* = .04)	+20 366 (*P* < .01)	0.70 (0.30-1.64)
Norepinephrine	+4.68 (*P* < .01)	+148.840 (*P* < .01)	2.89 (1.04-8.01)
Dopamine	−1.19 (*P* = .02)	+36 009 (*P* < .01)	0.99 (0.46-2.13)
Dobutamine	+2.31 (*P* < .01)	+28 992 (*P* < .01)	2.17 (0.88-5.32)
Milrinone	−1.04 (*P* = .13)	+52 754, (*P* < .01)	0.57 (0.23-1.42)
Vasopressin	−3.60 (*P* = .01)	−42 724 (*P* < .01	2.04 (0.54-7.70)
Complete repair of tetralogy of Fallot			
Epinephrine	+1.16 (*P* = .01)	+45 863 (*P* < .01)	0.89 (0.31-2.52)
Norepinephrine	+2.80 (*P* = .08)	+71 334 (*P* = .03)	5.37 (1.93-14.93)
Dopamine	+0.03 (*P* = .95)	+76 977 (*P* < .01)	4.01 (1.25-12.89)
Dobutamine	+4.50 (*P* < .01)	+14 533 (*P* = .47)	1.02 (0.31-3.31)
Milrinone	+0.23 (*P* = .79)	+30 071 (*P* = .09)	1.72 (0.20-14.24)
Vasopressin	−2.92 (*P* = .02)	−74 385 (*P* < .01)	1.73 (0.46-6.53)
Complete repair of total anomalous pulmonary venous connection			
Epinephrine	−2.15 (*P* = .26)	−30 874 (*P* = .32)	1.06 (0.49-2.32)
Norepinephrine	−0.69 (*P* = .82)	+47 945 (*P* = .33)	2.39 (1.28-4.45)
Dopamine	−2.36 (*P* = .18)	+47 382 (*P* = .10)	4.65 (2.28-9.50)
Dobutamine	+1.85 (*P* = .44)	−2845 (*P* = .94)	1.98 (1.12-3.48)
Milrinone	+0.14 (*P* = .94)	+15 367 (*P* = .64)	0.46 (0.23-0.91)
Vasopressin	−11.62 (*P* < .01)	−208 998 (*P* < .01)	1.60 (0.82-3.08)
Complete repair of common arterial trunk			
Epinephrine	+3.31 (*P* = .38)	+46 623 (*P* = .45)	0.94 (0.85-1.43)
Norepinephrine	+14.22 (*P* = .01)	+230 307 (*P* = .02)	0.91 (0.80-1.62)
Dopamine	−3.06 (*P* = .35)	+9562 (*P* = .86)	1.64 (0.09-28.61)
Dobutamine	+0.89 (*P* = .83)	+7443 (*P* = .91)	4.44 (0.55-35.75)
Milrinone	+2.51 (*P* = .53)	+79 384 (*P* = .23)	1.45 (0.84-4.48)
Vasopressin	−13.10 (*P* = .09)	−86 044 (*P* = .49)	1.32 (0.74-3.24)
Arterial switch			
Epinephrine	−5.24 (*P* = .02)	−7246 (*P* = .89)	0.59 (0.08-4.04)
Norepinephrine	+1.81 (*P* = .47)	+95 398 (*P* = .09)	8.14 (2.58-25.64)
Dopamine	+1.33 (*P* = .43)	+119 037 (*P* < .01)	2.53 (0.65-9.84)
Dobutamine	+1.75 (*P* = .52)	−13 716 (*P* = .82)	0.75 (0.08-6.62)
Milrinone	+3.13 (*P* = .21)	+104 369 (*P* = .07)	0.83 (0.11-6.00)
Vasopressin	−4.48 (*P* = .09)	−107 309 (*P* = .08)	1.07 (0.19-5.84)
Atrial switch			
Epinephrine	+0.39 (*P* = .65)	+34 569 (*P* = .07)	0.67 (0.04-9.96)
Norepinephrine	7.90 (*P* < .01)	+31 388 (*P* = .50)	6.32 (0.76-52.45)

(Continues)

TABLE 5 (Continued)

	Length of stay (days)	Billed charges (US dollars)	Inpatient mortality (OR, 95%CI)
Dopamine	−0.14 (*P* = .86)	+61 755 (*P* < .01)	2.58 (0.35-18.67)
Dobutamine	+1.86 (*P* = .33)	−15 470 (*P* = .71)	1.45 (0.07-27.36)
Milrinone	−0.14 (*P* = .88)	+25 431 (*P* = .22)	0.13 (0.01-1.40)
Vasopressin	+0.09 (*P* = .96)	−29 463 (*P* = .53)	5.22 (0.299-91.55)
Right ventricle to pulmonary artery conduit			
Epinephrine	−1.96 (*P* = .04)	+10 149 (*P* = .66)	0.93 (0.41-2.09)
Norepinephrine	+5.50 (*P* < .01)	+40 730 (*P* = .35)	4.78 (2.31-9.88)
Dopamine	−0.34 (*P* = .68)	+98 195 (*P* < .01)	1.13 (0.58-2.19)
Dobutamine	+3.11 (*P* = .02)	−32 509 (*P* = .33)	1.49 (0.63-3.48)
Milrinone	−0.97 (*P* = .37)	+21.007 (*P* = .42)	0.53 (0.23-1.24)
Vasopressin	−4.42 (*P* < .01)	−121 750 (*P* < .01)	3.17 (1.37-7.35)
Glenn			
Epinephrine	−0.05 (*P* = .92)	+10 191 (*P* = .32)	2.00 (0.91-4.39)
Norepinephrine	+4.36 (*P* < .01)	+138 927 (*P* < .01)	7.70 (3.90-15.18)
Dopamine	−1.99 (*P* < .01)	+13 192 (*P* = .18)	2.06 (1.11-3.85)
Dobutamine	+4.06 (*P* < .01)	+54 903 (*P* < .01)	2.67 (1.28-5.56)
Milrinone	+1.12 *P* = .16)	+36 244 (*P* = .01)	0.24 (0.11-0.50)
Vasopressin	−5.84 (*P* < .01)	−91 710 (*P* < .01)	8.28 (4.01-17.07)
Fontan			
Epinephrine	+0.06 (*P* = .87)	+10 191 (*P* = .32)	4.49 (1.47-13.63)
Norepinephrine	+1.68 (*P* = .03)	+138 927 (*P* < .01)	4.05 (1.91-8.58)
Dopamine	−0.02 (*P* = .93)	+13 192 (*P* = .18)	1.78 (0.88-3.58)
Dobutamine	+1.88 (*P* < .01)	+54 903 (*P* < .01)	1.45 (0.66-3.17)
Milrinone	−0.63 (*P* = .18)	+36 244 (*P* = .01)	1.00 (0.36-2.76)
Vasopressin	−1.50 (*P* = .01)	−91 710 (p <0.01)	3.01 (1.29-7.00)
Systemic to pulmonary artery shunt			
Epinephrine	−4.03 (*P* = .05)	−51 773 (*P* = .16)	1.04 (0.59-1.85)
Norepinephrine	+3.12 (*P* = .38)	+234 589 (*P* < .01)	5.89 (3.33-10.42)
Dopamine	−5.00 (*P* < .01)	+36 217 (*P* = .26)	1.59 (0.99-2.57)
Dobutamine	+9.50 (*P* < .01)	+69 690 (*P* = .13)	1.75 (1.03-2.95)
Milrinone	+1.20 (*P* = .55)	+116 502 (*P* < .01)	1.03 (0.61-1.74)
Vasopressin	−10.68 (*P* < .01)	−197 401 (*P* < .01)	5.28 (3.04-9.15)
Heart transplant			
Epinephrine	−22.84 (*P* < .01)	−555 814 (*P* < .01)	0.37 (0.06-2.32)
Norepinephrine	+1.89 (*P* = .710	+53 614 (*P* = .63)	5.69 (1.47-22.06)
Dopamine	−1.69 (*P* = .68)	+201 533 (*P* = .02)	4.17 (1.00-17.31)
Dobutamine	+11.11 (*P* = .03)	−40 572 (*P* = .72)	0.25 (0.03-1.78)
Milrinone	+15.01 (*P* = .02)	+334 382 (*P* = .02)	0.56 (0.07-4.15)
Vasopressin	−14.23 (*P* = .02)	−194 382 (*P* = .16)	4.86 (0.82-28.74)

are part of the pediatric health information system database and lends insight into the impact of these vasoactive agents on admissions characteristics.

When all admissions are considered together, milrinone was the most frequently used vasoactive agents with 81.4% use followed by epinephrine at 72.7%. The least frequently used vasoactive agents were vasopressin at 3.95% and norepinephrine at 3.3%. All vasoactive agents decreased in frequency of use through the course of the study period except for vasopressin which saw increased use. Dobutamine had the greatest decrease in use from 19.2% in 2004 to 1.7% in 2015.

These are interesting findings as they show the evolution of practice in critical care units caring for children after cardiac surgery. It appears that, with time, a larger proportion of postoperative patients are receiving no vasoactive agents thus allowing for all the vasoactive

agents frequencies to drop, except for that of vasopressin. The overall decrease in the use of vasoactive agents is likely due to improvements in perfusion and anesthesia strategies the perioperative period which lead to less myocardial depression (reference). During this era, a higher proportion of certain surgical procedures have also been done increasingly without the use of cardiopulmonary bypass which may also lead to decreased postoperative need for vasoactive agents (reference).

Additionally, decrease in specific vasoactive agents may also be due to change in the perceptions of what vasoactive agents are more optimal. For instance, dobutamine which showed the greatest decrease in use over the study period. This may be due to the increase in heart rate and myocardial oxygen consumption that is anecdotally noted and experimentally noted with dobutamine (reference). Additionally, vasoactive agents such as epinephrine and dopamine can provide the same, if not greater, inotropic effect at clinically equivalent doses.[6-8] The vasodilation that results from dobutamine can also be problematic and thus dobutamine may be increasingly avoided because of this as an additional reason.[8] While this study doesn't allow for delineation of the precise reason as to why dobutamine has fallen out of favor, the much greater decrease in its use compared to the other vasoactive agents does indicate that there is certainly a single or number of negative perceptions of dobutamine which have mediated at least some of this decrease.

A survey of pediatric intensivists managing postoperative cardiac patients assessed the self-reported use of vasoactive agents. This study found that from 98 respondents, 97% of them used milrinone, 45% used epinephrine, 38% used dopamine, and 11% used dobutamine for prevention of low cardiac output syndrome. While the exact numbers are not absolutely similar to the findings of this study, the preferential use of the agents is similar. This is not surprising since the current analyses, undoubtedly, have admissions during which inotropes were used for a variety of reasons not only the prevention of low cardiac output syndrome. Also, the survey consisted of international respondents, whereas the current analyses only captured admissions in the United States. The same survey then posed a separate question in which they assessed what vasoactive agents were used for treatment of low cardiac output syndrome, 42% said milrinone was their first choice, 36% epinephrine, 15% dopamine, and 2% dobutamine. Thus, once again a different clinical situation with a similar hierarchy of vasoactive agent preference.[2]

In the studied admissions, the mean number of inotropes utilized during a postoperative admission was 3. This does not mean that 3 vasoactive agents were utilized at the same time but simply means that 3 different vasoconstrictors were used at some point during the admission. When admission characteristics and outcomes were compared by looking at the total number of vasoactive agents used during the admission, length of stay, billed charges, and inpatient mortality all increased with a greater number of vasoactive agents. This likely represents a greater degree of illness in the admissions with a greater number of total vasoactive agents.

Of great interest was the independent association of specific vasoactive agents on inpatient mortality. The only vasoactive agents found to be associated with decreased inpatient mortality, for the entire cohort or any surgical subset, was milrinone. Milrinone was associated with decrease inpatient mortality for the entire cohort, complete repair of total anomalous pulmonary venous return, and the Glenn procedure. Milrinone was not found to be independently associated with increased mortality in any of the analyses. All other vasoactive agents were found to be independently associated with increased mortality for the entire cohort. In addition to this finding with respect to analyses done on the entire cohort, epinephrine was found to increase mortality in 1 surgical subset, norepinephrine in 10 surgical subsets, dopamine in 3, dobutamine in 3, and vasopressin in 3.

The interpretation of these results and the underpinnings of these findings is certainly not straightforward. Most certainly for both norepinephrine and vasopressin, which were used much less frequently than the other vasoactive agents, one could assume that the severity of illness of these patients was greater. Certainly, the number of surgical subsets in which norepinephrine was found associated with increased inpatient mortality seems to be consistent with this, as does the degree to which vasopressin increased inpatient mortality in the surgical subsets it did. Another consideration is that the specific hemodynamic effects of each vasoactive agents may negatively alter specific postoperative physiologies such as increasing systemic vascular resistance to augment arterial blood pressure after systemic to pulmonary artery shunt placement in a patient with parallel circulation who has pulmonary overcirculation. Nonetheless, with these factors in mind, it appears that off all the vasoactive agents other than milrinone, epinephrine consistently has less association with increased mortality.

The findings of increased mortality with vasoactive agents, although not necessarily noted in pediatrics before, has been demonstrated in the adult population. In the setting of acute heart failure, the use of vasoactive agents was documented to have increased mortality, a phenomenon that persisted at 6 months follow-up as well.[9] The issue of severity of illness once again arises in these studies and Mebazza and colleagues demonstrated that in patients with similar degrees of illness that those placed on vasoactive agents had increased mortality compared to those who didn't. This study also found that not all vasoactive agents had the same mortality profile, similar to the findings of this current study.[10]

While the length of stay and billed charges information is interesting, it is hard to put this in perspective with inpatient mortality. While developing some sort of combined metric of the 3 would be, theoretically, ideal the practical considerations make this more difficult. For instance, would there truly be a situation in which one would alter vasoactive agents use based on the cost it would take to save a pediatric life? Furthermore, would there be an upper limit to that cost where one would say a pediatric life is worth so much and above a certain cost one would no longer alter care? With the current culture of pediatric cardiothoracic and cardiac care this seems to be far from the case and thus this study includes these values but does not attempt to focus on them individually or attempt to combine them in any sort of fashion with inpatient mortality in a combined metric. If two vasoactive agents are found to have similar impacts on inpatient mortality then the agent with lower associated length of stay or billed charges would obviously have some benefits.

The data from these analyses in intriguing. Certainly, these data raise a few questions: (1) what are true indications for vasoactive support in the postoperative pediatric cardiac patient? and (2) what are the ideal vasoactive agents to be used for each specific indication? Unfortunately, this study is unable to answer these questions but highlights that these questions still exist after years of rapid evolution in the fields of pediatric cardiothoracic surgery and pediatric cardiology.

Designing studies to answer these questions may not be entirely intuitive either. One would have to select a surgical subset of patients, identify those with normal myocardial function immediately after the cessation of cardiopulmonary bypass, and then randomize these patients to an arm consisting of vasoactive support and an arm consisting of no vasoactive support. For those in the vasoactive support arm, a reasonable agent would seem to be milrinone based on the findings of this study and others. The study would then quantify how many patients in each arm go on to develop low cardiac output syndrome based on a reproducible clinical composite outcome (near-infrared spectroscopy, venous saturation, lactate, etc.) to determine if such prophylactic support was helpful. Undoubtedly, such a study would then present more questions to be answered to more finely tune the clinical approach. Then, this process would ideally be repeated for each surgical subset. With the introduction of hemodynamic systems that can now capture and store data from monitors in the intensive care unit in real-time, retrospective studies comparing those with and without vasoactive support may be able to provide some additional insight into the questions without having to use prospective studies described above.

This study is strengthened by having a large number of admissions across several centers in the United States. The large number of admissions allows for subset analyses by specific surgical procedures as well which offers additional insight. However, these analyses are not without their limitations. First, and foremost, there is no hemodynamic data at any time point in these admissions. Such data could help further classify degree of illness which simply cannot be done in this study. While the regression analyses conducted here can account for comorbidities such as heart failure or tachyarrhythmia, it does not capture the degree of systemic or diastolic ventricular dysfunction or the hemodynamic impact of a tachyarrhythmia. Thus, not being able to truly classify severity of illness also is a limitation of this analysis. Additionally, there is no information captured by the database regarding timing of initiation, duration, or dose of vasoactive agents used. Thus, no dose-dependent associations could be studied.

5 | CONCLUSIONS

The use of epinephrine, norepinephrine, dopamine, dobutamine, and milrinone in postoperative pediatric cardiac surgical admissions has decrease, while the use of vasopressin has increased. Even after controlling for demographic characteristics, cardiac lesions, and comorbidities, only milrinone was found to be associated with a decrease in inpatient mortality in any subset of these patients. The other vasoactive agents were actually associated with increased mortality in subsets of postoperative pediatric cardiac patients.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Study design, data review, data analysis, manuscript preparation: RL
Study design, data review, critical review of data analysis, manuscript review: SF

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