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Gabapentin as a novel adjunct for postoperative irritability after superior cavopulmonary connection operation in children

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Abstract

Objectives: Describing our institution's off-label use of gabapentin to treat irritability after superior cavopulmonary connection surgery and its impact on subsequent opiate and benzodiazepine requirements. *Methods:* This is a single-center retrospective cohort study including infants who underwent superior cavopulmonary connection operation between 2011 and 2019. *Results:* Gabapentin was administered in 74 subjects (74/323, 22.9%) during the observation period, with a median (IQR) starting dose of 5.7 (3.3, 15.0) mg/kg/day and a maximum dose of 10.7 (5.5, 23.4) mg/kg/day. Infants who underwent surgery in 2015–19 were more likely to receive gabapentin compared with those who underwent surgery in 2011–14 ($p < 0.0001$). Infants prescribed gabapentin were younger at surgery (137 versus 146 days, $p = 0.007$) and had longer chest tube durations (1.8 versus 0.9 days, $p < 0.001$), as well as longer postoperative intensive care (5.8 versus 3.1 days, $p < 0.0001$) and hospital (11.5 versus 7.0 days, $p < 0.0001$) lengths of stays. The year of surgery was the only predisposing factor associated with gabapentin administration in multivariate analysis. In adjusted linear regression, infants prescribed gabapentin on postoperative day 0–4 ($n = 64$) had reduced benzodiazepine exposure in the following 3 days (−0.29 mg/kg, 95% CI −0.52 – −0.06, $p = 0.01$) compared with those not prescribed gabapentin, while no difference was seen in opioid exposure ($p = 0.59$). *Conclusions:* Gabapentin was used with increasing frequency during the study period. There was a modest reduction in benzodiazepine requirements associated with gabapentin administration and no reduction in opioid requirements. A randomised controlled trial could better assess gabapentin's benefits postoperatively in children with congenital heart disease.

The superior cavopulmonary connection (SCPC), which includes the Glenn and hemi-Fontan operations, provides a stable source of pulmonary blood flow for children with single ventricle heart disease.[1,2] Even with an unobstructed course for passive blood flow from the upper half of the body to the lungs,[3] elevated pulmonary vascular resistance often leads to higher pressures in the SCPC circuit and can transmit to higher filling pressures affecting cerebral venous drainage.[4] This elevated pressure, sometimes referred to as "Glenn-head," can cause neuro-irritability and be challenging to manage. Providers at our institution sometimes prescribe gabapentin to manage perceived irritability in the postoperative period after SCPC. Gabapentin is an antiseizure medication frequently used for neuropathic and chronic pain treatment. It has also been suggested for acute pain management, as part of a multimodal approach.[5] Its mechanism of action is complex and remains unclear, but it notably involves the inhibition of voltage-gated calcium channels, thus decreasing neuronal excitability.[6] Gabapentin may thus be beneficial to reduce the headache and neuro-irritability following SCPC but has not been studied. In this retrospective study, we first aimed to describe our gabapentin prescription practices in infants following SCPC surgery, including typical dosing and changes in prescription practices over time. We also aimed to explore the impact of gabapentin on the administration of other medications used to address irritability, which include opioids and benzodiazepines.

Materials and methods

Study population and data collection

This study was approved by the Institutional Review Board (IRB) of the Children's Hospital of Philadelphia (IRB 18-015905) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to report our findings (Supplemental Table S1). Patients were identified through the institution's surgical database and included if the index operation (SCPC) was performed during the study period (May 2011–March 2019). We excluded subjects who remained intubated for more than 12 hours after arrival at the cardiac intensive care unit (CICU), as this is atypical in our institution and may have been indicative of a more complicated surgical and clinical course. For this first study, a convenience sampling method was used, and all consecutive patients matching our inclusion and exclusion criteria were included. Demographic, surgical, and pharmacologic information was extracted from the electronic medical record (EMR) Epic Inpatient product (Epic Systems, Inc., Verona, WI, USA) by trained analysts using structured query language. Collected data included patient age, gender, cardiac anatomy category, prior surgical history, known neurologic or genetic disorder, weight, dates and times of CICU admission and discharge, type of SCPC surgery (Glenn versus hemi-Fontan), chest tube durations, and intubation status at CICU admission (in our centre, most patients are extubated in the operating room prior to CICU admission following this procedure).

The observation period started at CICU arrival time and lasted until discharge or postoperative day 7, whichever came first. Collected pharmacologic data included the dates and times of administration and amounts of opiates, benzodiazepines, ketamine, dexmedetomidine, acetaminophen, ketorolac, and gabapentin administered over the first 7 days following surgery. Total exposure to different opioids and benzodiazepines was calculated by converting doses to morphine and midazolam equivalents, respectively.[7–9] For those who received gabapentin, the continuation of gabapentin following discharge was collected as a dichotomous variable.

Demographic and clinical characteristics were summarised using median (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. For continuous variables, medians were compared using the Wilcoxon–Mann–Whitney test. Categorical variables were compared using the chi-square test. Missing values were imputed using mean imputation so that they would be retained in the analysis. All analyses used two-sided tests and were performed using a nominal level of 0.05 for the threshold of significance. SAS (version 9.4; SAS Institute Inc.) and Stata SE Release 16 (College Station, TX: StataCorp LP) were used for analysis.

Primary statistical analysis

Two sets of analyses were completed for this patient cohort. First, we described the cohort of patients that received gabapentin on postoperative days 0–7 and the starting and maximum doses of gabapentin administered. We performed a multivariable analysis with logistic regression with variables that were significantly different ($p < 0.05$) on univariable analysis and occurred prior to possible gabapentin exposure to identify factors associated with gabapentin prescription during postoperative days 0–7.

Second, linear regression models were used to assess the association between gabapentin initiation during postoperative days 0–4 and requirements in opiates and benzodiazepines during postoperative days 5–7. Patients were grouped based on gabapentin administration on postoperative days 0–4 (binary exposure), and then total midazolam and morphine equivalent doses (per kg) on postoperative days 5–7 were compared between groups. The total daily doses (per kg) of opiates, benzodiazepines, ketamine, and dexmedetomidine received from postoperative days 0–4 were considered potential confounders and included in our adjusted models. Our multivariable linear regression models were also adjusted for other *a priori* defined potential confounders, including clinical and anatomic characteristics of the patients (Supplemental Table S2).

Secondary (sensitivity) analyses

A second set of multivariable linear regression models was performed using the log transformation of the total opioids and benzodiazepines doses received plus one (i.e., $\log[x + 1]$) as a sensitivity analysis to assess if a right-skewed distribution of outcomes impacted our results. These models were adjusted for the same covariates used in our primary analysis except for the four baseline medication variables; instead, log-transformed total medications (opioids, benzodiazepines, ketamine, and dexmedetomidine) doses (per kg) received on postoperative days 0–4 plus one were used. Lastly, both sets of linear regression models were performed but restricted to patients who were discharged from the hospital on postoperative day 5 or later ($n = 265$). This was done to evaluate if excluding patients who were discharged home early and were potentially less likely to receive any medication would impact our results.

Results

Study cohort

The initial cohort included 357 patients, but 34 patients were excluded: 31 due to prolonged postoperative intubation > 12 hours and 3 with missing data prohibiting complete analysis, leaving 323 subjects for analysis. Of those, 74 (22.9%) received gabapentin during postoperative days 0–7 (Table 1).

Gabapentin administration

Within our 7-day postoperative study window, the median postoperative day of gabapentin initiation was 2.2 (1.2, 4.3), and the median starting dose was 5.7 (3.3, 15.0) mg/kg/day (Supplemental Table S3). Titration of gabapentin occurred up to a maximum dose of 10.7 (5.7, 23.4) mg/kg/day reached after a median of 3.5 (2.0, 5.2) days. Gabapentin was continued after discharge in most subjects (54/74, 73.0%). Gabapentin use increased in the second half of the study period, with infants who underwent SCPC from 2015 to 2019 receiving more gabapentin compared to 2011–14 (28.7% versus 7.2%, respectively) (Fig. 1).

Characteristics of the patients who received gabapentin

Subjects prescribed gabapentin were more likely to be males ($p = 0.04$) and to have undergone a prior procedure ($p = 0.04$), younger at the time of SCPC (137 [121, 161] days versus 146 [129, 182] days, $p = 0.007$), weighed less at time of SCPC (6.0 [5.5, 6.8] kg versus 6.4 [5.7, 7.0] kg, $p = 0.04$), and had longer chest tube durations (1.8 [0.9, 2.8] days versus 0.9 [0.7, 1.9] days, $p < 0.001$)

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Table 1. Demographics based on gabapentin administered in the first 7 postoperative days[1]

	All (N = 323)	Gabapentin (N = 74)	No gabapentin (N = 249)	p-value[2]
Male (n, %)	198 (61.3)	53 (71.6)	145 (58.2)	0.04
Race (n, %)				0.13
Caucasian	187 (57.8)	48 (64.9)	139 (55.8)	
Black	48 (14.9)	5 (6.8)	43 (17.3)	
Asian and Pacific Islander	9 (2.8)	3 (4.1)	6 (2.4)	
Other	79 (24.5)	18 (79.3)	61 (24.5)	
Gestational age (weeks)	39 (38, 39)	39 (38, 39)	39 (38, 39)	0.39
Premature[3] (n, %)	29 (8.9)	8 (10.8)	21 (8.4)	0.53
Birthweight (kg)	3.20 (2.88, 3.50)	3.19 (2.76, 3.48)	3.20 (2.89, 3.51)	0.63
Chromosomal abnormality (n, %)				0.4
None	313 (96.9)	70 (94.6)	243 (97.6)	
Trisomy 21	2 (0.6)	1 (1.4)	1 (0.4)	
Other	8 (2.5)	3 (4.1)	5 (2.0)	
Major neurologic disorder (n, %)	39 (12.1)	11 (14.9)	28 (11.2)	0.40
Heterotaxy syndrome (n, %)	36 (11.2)	5 (6.8)	31 (12.4)	0.17
Anatomy (n, %)				0.15
Right ventricle-dominant	174 (53.9)	47 (63.5)	127 (51.0)	
Left ventricle-dominant	99 (30.7)	19 (25.7)	80 (32.1)	
Mixed	50 (15.4)	8 (10.8)	42 (16.9)	
Prior surgery (n, %)				0.04
None	28 (8.7)	2 (2.7)	26 (10.4)	
Norwood operation	179 (55.4)	49 (66.2)	130 (52.2)	
Shunt only	83 (25.7)	17 (23.0)	66 (26.5)	
Pulmonary artery banding	18 (5.5)	2 (2.7)	16 (6.4)	
Catheterisation-based procedure	9 (2.7)	4 (5.4)	5 (2.0)	
Other	6 (1.9)	0 (0.0)	6 (2.4)	
Type of SCPC (n, %)				0.50
Unilateral bidirectional Glenn	243 (75.2)	54 (73.0)	189 (75.9)	
Bilateral bidirectional Glenn	36 (11.1)	7 (9.5)	29 (11.6)	
Hemi-Fontan	44 (13.6)	13 (17.6)	31 (12.4)	
Age at SCPC (days)	142 (127, 173)	137 (121, 161)	146 (129, 182)	0.007
Weight at SCPC (kg)	6.3 (5.7, 7.0)	6.0 (5.5, 6.8)	6.4 (5.7, 7.0)	0.04
Total CPB (min)	53 (35, 68)	59 (38, 70)	53 (34, 68)	0.17
Postoperative chest tube duration (days)	1.0 (0.8, 1.9)	1.8 (0.9, 2.8)	0.9 (0.7, 1.9)	<0.001
Hospital length of stay (days)	8.0 (6.0, 15.0)	11.5 (7.0, 36.0)	7.0 (5.0, 11.0)	<0.001
CICU length of stay (days)	3.2 (2.1, 5.2)	5.8 (3.0, 11.0)	3.1 (2.1, 4.9)	<0.001
Year at SCPC				<0.001
2011[4]	24 (7.4)	1 (1.4)	23 (9.2)	
2012	37 (11.5)	5 (6.8)	32 (12.6)	
2013	59 (18.3)	7 (9.5)	52 (20.9)	
2014	32 (9.9)	1 (1.4)	31 (12.4)	
2015	35 (10.8)	7 (9.5)	28 (11.2)	
2016	42 (13.0)	9 (12.2)	33 (13.3)	

(*Continued*)

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Table 1. (*Continued*)

	All (N = 323)	Gabapentin (N = 74)	No gabapentin (N = 249)	p-value[2]
2017	44 (13.6)	18 (24.3)	26 (10.4)	
2018	40 (12.4)	22 (29.7)	18 (7.2)	
2019[4]	10 (3.1)	4 (5.4)	6 (2.4)	

CICU = cardiac intensive care unit; CPB = cardiopulmonary bypass; SCPC = superior cavopulmonary connection.
[1]Values are presented as median (IQR) unless otherwise specified.
[2]P-values calculated from chi-square tests (categorical covariates) or Wilcoxon rank-sum tests (continuous covariates).
[3]Prematurity is defined as <37 weeks gestational age.
[4]Incomplete data.

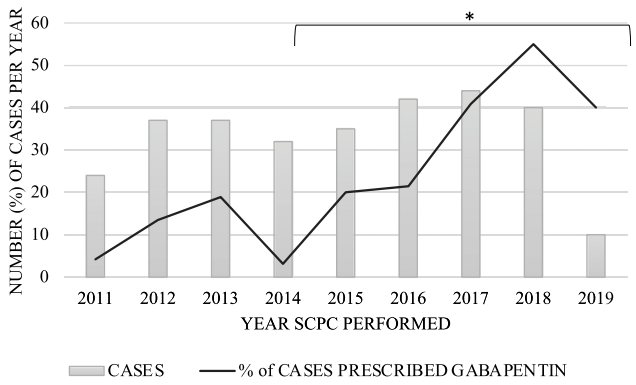

Figure 1. Trends in gabapentin prescription over time, from 2011 to 2019. Gray bars indicate a number of SCPC cases per year, black line indicates the percentage of SCPC cases receiving gabapentin. Bracket over the years 2015–2019 indicates a higher rate of gabapentin prescription (* p=<0.0001). Data for 2014 and 2019 are incomplete. SCPC = superior cavopulmonary connection.

and longer CICU (5.8 [3.0, 11.0] days versus 3.1 [2.1, 4.9] days, $p < 0.0001$) and hospital (11.5 [7.0, 36.0] days versus 7.0 [5.0, 11.0] days and $p < 0.0001$) lengths of stay (LOS) (Table 1). Otherwise, there were no significant differences between the cohorts.

Variables reaching our significant threshold in univariate analysis and included in the multivariable analysis included male sex, prior surgery, age at SCPC, weight at SCPC, and year of SCPC (Supplemental Table S4). Only the year of surgery retained significance in the multivariable model.

Impact of gabapentin on total opioids and benzodiazepines requirements

A total of 60 infants received gabapentin on postoperative days 0–4 (Supplemental Table S5). The adjusted multivariable linear regression models showed that receiving gabapentin on post-operative days 0–4 was associated with a slight decrease in total midazolam equivalent doses (estimate −0.29, [95% CI −0.52, −0.06], $p = 0.012$) on postoperative days 5–7, but no difference in total morphine equivalent doses over the same period (estimate −0.11, [95% CI −0.52, 0.30], $p = 0.59$) (Table 2). Multivariable linear regression models with the log-transformed outcome yielded similar results: Gabapentin was associated with a 7.2% decrease in total midazolam equivalent requirements (transformed beta = −0.072, 95% CI: [−0.13, −0.010], $p = 0.02$), with no difference in opioids requirements (transformed beta = 0.025, [95% CI −0.056, 0.11], $p = 0.55$) (Supplemental Table S6). Multivariable linear regression models using the subset of patients discharged on postoperative day 5 or later (n = 265) showed similar results (Supplemental Table S7).

Discussion

To our knowledge, this is the first study to report the use of gabapentin in postoperative paediatric cardiac patients, specifically after SCPC. In our retrospective cohort, 22.9% of infants following SCPC received gabapentin, with an increased likelihood of receiving gabapentin in more recent years. Infants receiving gabapentin appeared sicker; they were younger, more likely to have undergone a previous procedure, and had longer chest tube durations and CICU and hospital LOS. Gabapentin administration in the 4 initial postoperative days led to a decrease in benzodiazepine exposure over the following 3 days but did not decrease opiate exposure.

Non-opioid adjuncts have been explored in various patient populations to treat postoperative pain and decrease opioid use. Gabapentinoids, which include gabapentin and pregabalin, are commonly used to manage neuropathic and chronic pain and have been proposed for postoperative pain. Gabapentinoids are gamma-aminobutyric acid (GABA) analogues but have no direct effect on GABA receptors, and their analgesic effect is mediated mainly through voltage-gated calcium channels. In animal models, gabapentin was found efficient in treating inflammatory and postoperative pain, and its combination with opioids provided a synergistic effect.[6] In adults, gabapentin has successfully been used to manage headache symptoms.[10] Therefore, its use as part of a multimodal analgesic strategy is particularly appealing following SCPC, where cerebral venous congestion and resulting headache may contribute to patients' discomfort.

In paediatrics, the use of gabapentin is mostly reported in neonates with irritability and agitation of various origins,[11,12] in children with neuropathic pain,[13–15] and in paediatric oncologic diseases.[16] When narrowing the focus on perioperative patients, there are limited data. A randomised trial evaluated the use of gabapentin in children following the Ravitch procedure (surgery performed for the treatment of pectus excavatum), and although gabapentin did not demonstrate any reduction in postoperative pain scores, it was associated with reduced postoperative anxiety scores.[17] More commonly, gabapentin has been studied after paediatric orthopaedic procedures, such as spinal fusion and scoliosis repair, with mixed results. While some studies demonstrated reductions in pain scores and opioid administration,[18–21] others showed conflicting results with lower pain scores but no reduction in opioid use,[22] or simply no benefits of the addition of gabapentin on perioperative pain or opioid prescription.[23]

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Table 2. Impact of gabapentin administration on postoperative days 0–4 on opioid and benzodiazepine requirements on postoperative days 5–7 using adjusted linear regression (n = 323)

	Linear regression	
	Estimate (95% CI)	p-value
Total morphine equivalent (mg/kg) on postoperative days 5–7		
Unadjusted effect of gabapentin	0.52 (−0.83, 1.13)	0.09
Effect of gabapentin adjusted only for baseline opiates	−0.002 (−0.40, 0.39)	0.99
Adjusted effect of gabapentin	−0.11 (−0.52, 0.30)	0.59
Total midazolam equivalent (mg/kg) on postoperative days 5–7		
Unadjusted effect of gabapentin	0.11 (−0.24, 0.47)	0.53
Effect of gabapentin adjusted only for baseline benzodiazepines	−0.26 (−0.53, −0.006)	0.06
Adjusted effect of gabapentin	−0.29 (−0.52, −0.06)	0.01

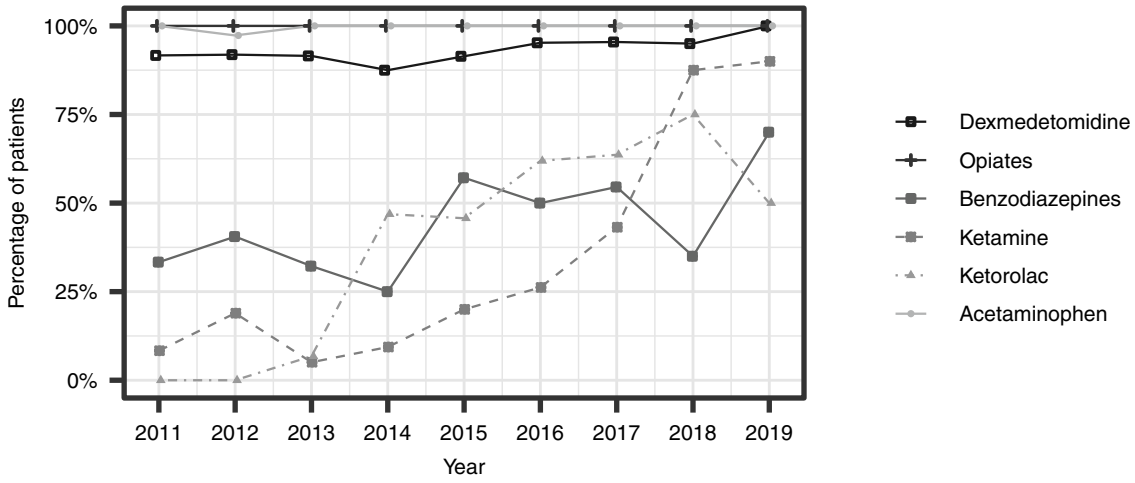

Figure 2. Percentages of patients exposed to different analgesics and sedatives over time. Data for 2014 and 2019 are incomplete.

This study is the first to report gabapentin dosing practices in paediatric patients following SCPC. The frequency and steps in which gabapentin doses are increased are not standardised at our institution, thus making our analysis and the interpretation of our results difficult. The median starting dose used in this study (5.7 mg/kg/day) is consistent with published literature for the management of postoperative, cancer-associated, and neuropathic pain,[24–27] with described initial neonatal and paediatric doses of 5–20 mg/kg/day. However, the maximum daily dose of gabapentin in our study (10.28 mg/kg/day) was lower than previously described in the available paediatric literature (usual dosing range 20–30 mg/kg/day, possible titration up to 72 mg/kg/day),[28] which might have impacted our results. Additional dose titrations occurring outside of our study period and prior to discharge may, however, have occurred but were not captured in this study. The continuation of gabapentin after the first initial 7 postoperative days was not examined, other than if the medication was prescribed at the time of discharge.

Analgesics and sedatives prescription practices over time are depicted in Figure 2 and Figure S1. Acetaminophen, opiates, and dexmedetomidine were consistently used in most patients (nearly 100% for acetaminophen and opiates and > 80% for dexmedetomidine). At the beginning of the study period, our CICU did not have a formalised sedation and analgesia pathway, although one was in development and ultimately implemented in 2014. This original pathway recommended specific agents, doses, and dose titrations based on patient age and comorbidities, with a combination of acetaminophen, opioids, and dexmedetomidine being the cornerstone of therapy. As new evidence was published and prescribing practices changed, the pathway was updated to include additional agents, and the use of ketorolac and ketamine increased. Interestingly, our institution has a long-standing benzodiazepine-sparing policy. Indeed, the total benzodiazepine doses and percentages of patients receiving benzodiazepines did not decrease over the study period, strengthening our findings (Fig. 2 and Fig. S1).

Although gabapentin was, and continues to be, used outside of the pathway, its prescription increased over our study period, nearly quintupling over 8 years. This resulted in a patient having 47-fold odds of being prescribed gabapentin if their SCPC took place in 2018 compared to 2011. There also has been an increase in gabapentin use over a similar period in other patient populations.[12] As literature was added to the field, gabapentin may have gained favourable opinion over recent years because of its safety and possible benefits.[29] This likely led to increased use and clinicians becoming more comfortable prescribing it over time, further

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accentuating this trend. In the current study, individual clinician practices may have been variable due to different comfort levels with this medication. However, accurate prescriber-related information was not available, and clinician-dependent variability could not be evaluated.

In contradiction with previous studies,[18–20] we were unable to identify a reduction in opiate exposure associated with gabapentin, although a modest impact on subsequent benzodiazepines prescription was identified (effect size = –0.29 mg/kg over the following 3 days). The retrospective nature of our study and the fact that gabapentin use was not standardised may have limited our ability to demonstrate gabapentin's effects on sedatives and analgesics requirements. Indeed, considerable clinical differences existed between the cohorts who received gabapentin and those who did not. Based on the profile of younger infants more likely to have had a prior palliative procedure, subjects receiving gabapentin appear to have constituted a higher-risk population, more likely to have been previously exposed to opioids. We believe gabapentin was used preferentially in subjects with more irritability and inadequate sedation and analgesia, possibly in part due to previous opiate exposure and secondary tolerance. Unfortunately, pain and sedation scores were inconsistently done and recorded, and we could not confirm this hypothesis or evaluate the effect of gabapentin on patients' comfort. Furthermore, hemodynamics and echocardiographic data or other postoperative factors that could contribute to pain and discomfort were not available and could not be included in our analysis. Specifically, we did not directly assess for clinical concerns for superior caval vein (SVC) syndrome (notably elevated central venous pressure), which some providers consider the main off-label indication for gabapentin. However, we were able to get an indirect marker of SVC syndrome in the form of chest tube durations. The increased chest tube duration in infants receiving gabapentin, although modest (1.8 days versus 0.9 days), suggests a higher SCPC pressure and increased probability of neuro-irritability.

Study limitations

Because of the retrospective design of this single-center study, we recognise some important limitations. Our gabapentin prescription practices were not standardised, and thus patient selection and dosing varied significantly. As mentioned above, we were unable to collect the indication for gabapentin initiation (pain, irritability, or other symptoms) and did not have consistent measurements of pain scores to assess the impact that gabapentin had on these. We limited our assessment to 7 days after SCPC, as this was our previously reported median hospital LOS after SCPC,[30] but given that subjects prescribed gabapentin had longer LOS, we may have limited our window for evaluation. Furthermore, due to difficulties in matching the cohorts, patients were grouped based on gabapentin prescription during postoperative days 0–4, creating variable duration of follow-up for later opiates and benzodiazepines dosing during postoperative days 5–7. Similar to other observational studies, this study may also lack unmeasured confounders for assessing the potential benefits of gabapentin. Finally, the reproducibility of our results in other settings remains to be determined. Despite these limitations, our study also has significant strengths. This is the first report describing the use of gabapentin in children following cardiac surgery, specifically SCPC.[31] Due to the high surgical volume of our center, we were able to gather a relatively large sample size, given the rarity of the disease. This allowed us to demonstrate a modest but clinically significant reduction in benzodiazepines requirements associated with gabapentin use, which appears independent from a generalised benzodiazepines reduction over the years considering our institutional benzodiazepines-sparing sedation practices over the study period.

Conclusion

In this first description of gabapentin use after SCPC, we found that gabapentin administration increased over the past decade in our institution. Patients prescribed gabapentin had longer chest tube durations and longer hospital and CICU LOS, and the only identified predisposing risk factor associated with its use was the year SCPC was performed. Patients prescribed gabapentin had a modest reduction in subsequent benzodiazepines total dose, but no effect was seen on opioids' requirements. Our results are mostly hypothesis generating and lead the way for future studies, which should consider the use of large healthcare databases providing rich variable measures and a randomised controlled approach to better determine the potential effects and benefits of gabapentin in this population.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124024983.

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Competing interests. None.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the IRB of our institution.

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