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Postoperative opioid administration and post-traumatic stress symptoms in preschool children after cardiac surgery

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ABSTRACT

Purpose: The purpose of this study was to explore relationships between postoperative opioid administration and posttraumatic stress symptoms (PTSS) in preschool-aged children surviving cardiac surgery.
Design and methods: This was a cross-sectional, descriptive study using survey administration and medical chart review. Primary caregivers of children aged three to six years who underwent cardiac surgery at our institution between 2018 and 2020 were invited to participate. Opioid administration was calculated according to morphine milligram equivalents and indexed to the child's body weight. Caregivers completed the Young Child Posttraumatic Stress Disorder Checklist to explore child PTSS. We used correlational methods to assess the strength and direction of relationships between postoperative opioid administration and child PTSS.
Results: We did not find a statistically significant relationship between total postoperative opioid administration and child PTSS. When analyzing individual opioid agents, morphine did show a significant inverse relationship to YCPC scores ($r_s = -.57$, $p = .017$) in children with single ventricle physiology.
Conclusions: Total postoperative opioid administration was not statistically significantly related to child PTSS in our sample. Differing patterns of association were noted among children with single- versus bi-ventricular physiology. Postoperative morphine administration was favorably associated with PTSS in children with single-ventricle physiology.
Practice implications: Nurses caring for preschool children who undergo cardiac surgery should anticipate the potential development of PTSS in their patients. Studies using larger sample sizes and longitudinal design are needed to replicate the significant relationship between morphine administration and PTSS in preschoolers with single-ventricle physiology.

Background

Post-traumatic stress disorder (PTSD) is a constellation of persistent, disordered stress responses following exposure to a traumatic event and may arise as a potential complication of traumatic medical experiences (American Psychiatric Association, 2013; Christian-Brandt et al., 2019; Kassam-Adams et al., 2005; Meentken et al., 2017). In preschool children, post-traumatic stress symptoms (PTSS) are organized into four categories (intrusion, avoidance, negative alterations in cognition, and alterations in arousal and reactivity) which follow exposure to trauma. Children in this age group may exhibit developmental regression, constriction in play, new fears of previously tolerated situations or objects, and increased clinginess to caregivers as an expression of PTSS. When symptoms persist for at least four weeks and lead to functional impairment, children may meet criteria for diagnosis of PTSD (American Psychiatric Association, 2013; De Young & Landolt, 2018; Simonelli, 2013).

Researchers have investigated contributing factors to the development of post-traumatic stress to identify patients who are most vulnerable to PTSD. For example, in young children, previous studies have shown that parental psychopathology, including parental PTSD, is more closely associated with child PTSD than any child demographic characteristics (Dow et al., 2012; Schechter et al., 2017; Scheeringa et al., 2015). Additionally, pain has been associated with PTSD in both pediatric and adult patients following injury and medical procedures (Archer et al., 2016; Connolly et al., 2004; Franck et al., 2015; Gold et al., 2008; Norman et al., 2008; Ravn et al., 2018). Previous research

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has examined the relationship between pain and post-traumatic stress and the potential utility of psychopharmacologic interventions to limit the development of posttraumatic stress responses after traumatic injuries or medical experiences (El-Gabalawy et al., 2019; Mouthaan et al., 2015; Sheridan et al., 2014). Opioid administration following acute painful events such as trauma, burn injury, or surgery has been associated with favorable impact on PTSD in adults and in both school-aged and preschool children, thought to be related to the effects of opioid agents on memory consolidation and fear-conditioning responses (Holbrook et al., 2010; Saxe et al., 2001; Stoddard et al., 2009; van Marle, 2015). Preschool-aged children who survive cardiac surgery – a growing population in the wake of medical and surgical advancements for treatment of congenital heart disease (CHD) - may similarly be vulnerable to post-traumatic stress (Jacobs et al., 2016). The diagnosis of PTSD in this age group remains challenging, and children may suffer from PTSS even in the absence of a clinical diagnosis (De Young & Landolt, 2018; Gigengack et al., 2015). Our study, therefore, explored reports of PTSS in preschool children surviving cardiac surgery rather than children who had received a diagnosis of PTSD. Currently, there are no known studies investigating the relationship between postoperative opioid administration and PTSS in this population.

Purpose

The purpose of this study was to examine the relationship between postoperative opioid administration and PTSS for preschool children three to six years of age surviving cardiac surgery.

Literature synthesis

Until recently, PTSD was difficult to conceptualize in preschool children because the diagnostic criteria were not appropriate for typical developmental capabilities in children less than six years of age (De Young et al., 2011a, 2011b; De Young & Landolt, 2018; Pai et al., 2017). In the fifth edition of the APA's Diagnostic and Statistical Manual, behaviorally anchored criteria intended for PTSD diagnosis in early childhood helped to clarify this phenomenon in children under age six. However, preschool-aged children remain at risk for under-recognition of PTSD and, therefore, inadequate treatment, due to the difficulty of assessing highly internalized symptoms in children who have not developed the verbal skills to detail their internal state (Scheeringa et al., 1995).

Children with post-traumatic stress in early childhood and untreated PTSD are at risk for long-term mental health complications, poor medical compliance, decreased family and societal functioning, and impaired cognitive and developmental outcomes (Copeland et al., 2018; Delamater & Applegate, 1999; Grasso et al., 2013; Van der Kolk, 2015). These risks are particularly problematic for children who require cardiac surgery, as lifelong medical follow-up is required and many are already at risk for poor neurocognitive outcomes when compared with healthy peers (Cassidy et al., 2018; Deng et al., 2016; Gleason et al., 2019; Ilardi et al., 2020).

PTSD has been operationalized in the literature both as a dichotomous variable (whether a patient met diagnostic criteria) and a continuous score of post-traumatic stress symptoms (PTSS). Individuals may display PTSS even if they do not meet the diagnostic criteria for PTSD, although there is no consistent definition for "subthreshold" PTSD (Meentken et al., 2017). PTSD is a complicated phenomenon, impacted by factors both internal and external to the individual; in the setting of traumatic medical experiences, these may include the individual's appraisal of the traumatic event and painful experience (Marsac et al., 2017).

Pain and post-traumatic stress

Young children who experience pain after cardiac surgery may be at risk for the development of post-traumatic stress, as pain is frequently associated with post-traumatic stress in both pediatric and adult literature (Holbrook et al., 2010; Nikbakhtzadeh et al., 2020; Ravn et al., 2018; Stahlschmidt et al., 2020). Pain and post-traumatic stress may reciprocate one another through excessive emotional stimulation and fear-conditioning responses (Hildenbrand et al., 2018). Researchers suggest that pain may serve as a reminder of the traumatic event, a trigger for unpleasant memories, or a component of abnormally-heightened physiologic responses (Gold et al., 2008).

Unfortunately, pain itself is difficult to operationalize in the setting of pediatric cardiac surgery. Inpatient pain assessment for the preschool patient is reliant upon the child's ability to endorse pain and nursing interpretation and documentation of pain. Previous research has demonstrated extensive variability in pain assessment for pediatric patients requiring hospitalization (Laures et al., 2019). Young children are often sedated postoperatively and may require chemical paralysis, rendering them physically unable to provide subjective pain scores. In addition to being inconsistently available in the medical record, pain assessment using standardized measures may fluctuate for individual patients throughout their hospitalization. For example, pain may be documented according to subjective nursing assessment (i.e. "pain assumed," Laures et al., 2019) while the child is receiving sedative medications immediately postoperatively, and then may transition to a developmentally appropriate visual analog scale at later points within the same hospitalization as their mentation normalizes. Further compounding the difficulty with pain documentation, agitation and delirium may yield symptoms which mimic pain responses and may themselves be worsened by insufficiently treated pain (Pandharipande et al., 2017).

While the utility of physiologic markers for the assessment of both pain and PTSS has been discussed in the literature, these may also be unreliable in the post-operative cardiac surgery population (Bryant et al., 2000; Kassam-Adams et al., 2005; Marsac et al., 2017; Pitman et al., 2012; Stoddard et al., 2006). Heart rate, for example, is not a feasible proxy for pain assessment in this setting, as it may be affected by altered electrical conduction, vasoactive medications, or changes in hemodynamic status which are unrelated to pain.

Opioid administration and post-traumatic stress

Given the limitations noted with pain assessment in hospitalized young children, opioid administration may serve as a useful surrogate for the operationalization of pain in this population and has been used as an independent variable in previous studies (Saxe et al., 2001; Stoddard et al., 2009). Relationships between opioid administration and PTSS have been variable in the literature. According to Stoddard, et al., higher doses of opioids delivered to preschool children with burn injuries have been associated with fewer PTSS burden post-discharge, but this study used a very small sample size ($N = 11$, Stoddard et al., 2009). Other researchers have described a similar favorable impact on PTSS with opioid administration in an acute care setting (Holbrook et al., 2010; Nixon et al., 2010; Sheridan et al., 2014). These findings were not reproduced in a study investigating morphine administration and school-age children after unintentional traumatic injuries (Hildenbrand et al., 2018). Researchers have interpreted higher morphine doses as presumably better pain control and have suggested that, in addition to acting on pain, morphine may inhibit neurobiological fear conditioning processes (Szczytkowski-Thomson, Lebonville, & Lysle, 2013, (Abdullahi et al., 2020). There is conflicting evidence for the impact of other, non-morphine opioid drugs on emotion and fear responses (Wardle et al., 2014). While research is ongoing for potential interventions, including cautious use of psychopharmacologic agents, to reduce PTSS after traumatic events in early childhood, this has not yet been extended to preschool-aged children after cardiac surgery (Wolmer et al., 2017).

Conceptual framework

This study was part of a larger project examining potential biological, psychological, and social contributors to post-traumatic stress

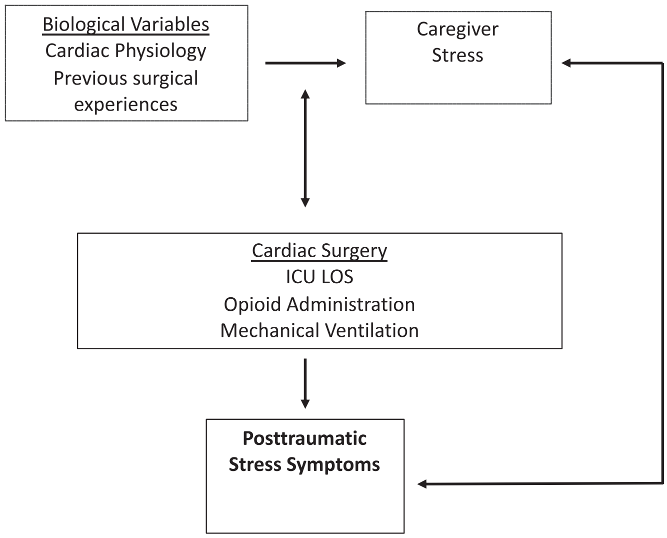

Fig. 1. Conceptual model.

symptoms in preschool children after cardiac surgery. The conceptual framework (see Fig. 1) guiding the overall project was based on the work of Marsac and colleagues, who proposed a biopsychosocial framework for understanding post-traumatic stress in children who experience traumatization due to medical events (Marsac et al., 2014). For our work, we operationalized the environmental context of cardiac surgery as ICU LOS, opioid administration, and mechanical ventilation. Opioid administration is a modifiable variable related to cardiac surgery and the associated postoperative care, and was the primary independent variable for the current study. In accordance with the literature, we have not attempted to restrict the definition of a potentially traumatic "medical event" beyond "cardiac surgery" and the implied environmental context of the surgery, as children in this age group are prone to catastrophizing even minor procedures and lack the cognitive capability to asses risk (Drury et al., 2013; Pai et al., 2017).

Methods

Sample

Institutional Review Board approval was obtained prior to the study. Data collection occurred at an academic medical center in the southeastern United States where more than 500 cardiac surgical cases are performed annually. Postoperative pain and sedation management protocols at our institution are generally determined based on whether the child arrives to the ICU with an open or closed sternum and, if closed, whether extubation is anticipated within the first 24 hours postoperatively. In addition to opioid agents, postoperative patients receive scheduled acetaminophen and NSAIDs for the first 24 - 48 hours postoperatively, unless contraindicated. Continuous opioid infusions are not routinely administered if extubation is planned within the first 24 hours, although this varies at the discretion of the ICU physician or advanced practice provider. Dexmedetomidine is the preferred sedative agent at our institution, and benzodiazepine infusions are not used in the immediate postoperative period.

We reviewed our institution's surgical caseload from 2018-2020 to screen for eligible participants. Sample size determination was largely based on the anticipated number of participants eligible for the study at our institution and observed recruitment rate during an earlier pilot study undertaken by the principal investigator (PI). Nevertheless, we performed a power analysis and determined that a sample size of at least 40 participants would enable detection of correlations as small as 0.42 (respective Cohen's d = 0.93, 80% statistical power, alpha = .05).

Eligible participants included parents or caregivers with children between three years and six years of age, with cardiac surgery occurring in the past two years and at least four weeks prior to study onset. Caregivers of children who received interventional procedures only (i.e., cardiac catheterizations or electrophysiology studies) were excluded. Eligible caregivers were at least 18 years of age and able to speak and understand English. Caregivers included biological mothers and fathers, adoptive parents, and legal guardians. Participants were excluded if the child died prior to study onset, the child was inpatient at the time of data collection, or there was an open DCS investigation.

After we reviewed our institution's surgical caseload, 139 patients and their caregivers were screened for further eligibility based upon the child's age. The PI successfully contacted fifty-three of the remaining 117 eligible participants. Of those, 44 (83%) enrolled in the study. Subsequently, it was determined that one child did not have a postoperative intensive care stay, resulting in an analysis sample of $N = 43$ children and their caregivers.

Measurement

Post-traumatic stress symptoms

The Young Child PTSD Checklist (YCPC) is a developmentally sensitive caregiver-report survey designed to evaluate post-traumatic stress symptoms in young children between one and six years of age (MS Scheeringa, 2014). It has been updated for DSM-V. The 42-item YCPC is an abbreviated version of the PTSD module of the Diagnostic Infant and Preschool Assessment (DIPA), which was been successfully used in early childhood psychiatric and mental health research. The YCPC has demonstrated strong psychometric properties in the literature, with good internal consistency ($\alpha = .77$) and concurrent criterion validity when compared to the PTSD module of the DIPA (Haag & Landolt, 2017; Scheeringa, 2020). The internal consistency of the scores in this study was considerably higher with a Cronbach's $\alpha = 0.94$.

Opioid administration

The PI reviewed electronic medical records to determine the doses of opioid drugs administered during children's postoperative ICU stay. Standardization of opioid dosing has been cited frequently in the literature. Using methods described by Saxe et al. (2001) and Stoddard et al. (2009), opioid medications were converted to morphine milliequivalent dosing (MMEs) and then indexed to the child's weight and duration of ICU stay. Medications were compared in terms of MMEs/kg/day. The following medications were included in the calculation: hydromorphone, morphine, oxycodone, and fentanyl. No children in this sample received methadone, commonly used in our institution for iatrogenic opiate withdrawal, and the drug was therefore excluded from analysis.

Procedure

Data collection occurred over 11 weeks from September to December 2020. The PI mailed introductory letters describing the study to potential participants. Contact information was provided for caregivers who wished to opt-out of further communication about the study; otherwise, the PI contacted potential participants via telephone within 7-10 days of mailing letters to further describe the study. No potential participants proactively opted out of the study, and therefore the PI attempted to contact all eligible caregivers. After obtaining verbal consent from interested caregivers, we distributed consent forms and study materials via electronic REDCap survey (Harris et al., 2009; Harris et al., 2019). Participants completed demographic questionnaires and the YCPC. The PI reviewed the electronic medical record to collect information about the child's postoperative course, including opioid administration and underlying cardiac physiology.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (26). We used frequency distributions to summarize nominal data. Means and standard deviations were calculated to summarize normally distributed continuous data, otherwise we used medians and inter-quartile ranges. We tested for between-group differences using student's t-test (normally distributed data), Mann-Whitney U tests (non-normal continuous data) and Chi-square tests of independence (categorical). The strength of the relationships between opioid administration and YCPC scores were assessed using Spearman's *rho* correlations. We used $p < .05$ for determining statistical significance.

Findings

Characteristics of the 43 children and caregiver participants are shown in Table 1. Children were a median 55.2 months old (IQR 18, 69) and had surgery at a median 40.4 months of age (IQR 27.2, 47.6). Approximately half of the children were male (51.2%), and a majority of the caregiver survey respondents ($n = 39$, 90.7%) were female. Seventeen (39.5%) of the children had single ventricle cardiac physiology. Children with single ventricle physiology were significantly older at the time of surgery than their bi-ventricle counterparts (median 45.5 months versus 29.2 months, $p = .007$). There were otherwise no significant demographic differences between children with single or bi-ventricular cardiac physiology. Median duration of postoperative ICU stay was significantly longer for children with single ventricle physiology than those with biventricular physiology (5 days vs 2 days, respectively; $p < .001$). Very few children with biventricular physiology had experienced any prior surgeries, while children with single ventricle physiology had a median of 3 prior surgeries ($p < .001$) (Table 1) .

Summaries of the opioid administrations and YCPC scores are presented in Table 2. Based on medical chart review, no children were receiving opioid medications at the time of presentation for the index cardiac surgery. While not necessarily receiving an opioid drug every day during their postoperative ICU stay, all children received at least one opioid drug at some time during their stay. Morphine was the most commonly administered opioid drug with only six children not receiving at least one dose of morphine. Opioid administration during participants' ICU stay ranged from 0 - 3.99 MME/kg/day (median = 0.5). When not indexed to the child's weight or ICU LOS, the total MMEs administered ranged from 0 – 369.8 MMEs (median = 9.1). YCPC scores ranged from 0 to 56 of a possible maximum score of 92 (median = 6.0). Five (11.6%) participants had a YCPC score of 26 or higher, which is the threshold for a probable diagnosis of PTSD (Scheeringa, 2014).

We observed no statistically significant correlations of total MMEs administered or MMEs/kg/day delivered with YCPC scores ($r_s = 0.27$ and 0.11 respectively, $p > .05$, see Table 3). For the entire sample, we found a very small and not statistically significant correlation between the quantity of morphine administered and YCPC scores ($r_s = -.07$, $p = .643$). Children with single ventricle physiology generally have different healthcare experiences than children with two cardiac ventricles, including greater number of cardiac surgeries, longer hospitalizations, and more frequent non-cardiac comorbidities (Davis et al., 2008; Golfenshtein et al., 2019; Ricci et al., 2021). Therefore, we grouped the children according to their cardiac physiology and analyzed correlations between key variables within each group. We found a statistically significant inverse relationship between morphine and YCPC scores in the group of children with single ventricle physiology ($\rho = -.57$, $p = .017$), yet that association in bi-ventricle patients was much smaller, in the opposite direction, and not statistically significant $r_s = .21$, $p = >.05$). No such differing patterns were observed for the other opioid drugs included in this study (see Table 3).

Table 1
Sample characteristics (N = 43).

	Sample (N = 43)	Univentricular Physiology (n = 17)	Biventricular Physiology (n = 26)	p-value
Child Characteristics	Median (IQR)			
Current age (months)	55.2 (48.9, 68.7)	56.3 (49.8, 72.2)	54.1 (45.8, 62)	.214
Age at surgery (months)	40.4 (27.2, 47.6)	45.5 (36.9, 51.2)	29.2 (21.9, 43.4)	**.007**
ICU length of stay (days)	2 (1, 4)	5 (2, 9)	1 (1, 2)	**<.001**
Number of prior surgeries	1 (0, 3)	3 (2, 4)	0 (0, 1)	**<.001**
Gender	**N (%)**			.850
Female	21 (48.8)	8 (47.1)	13 (50)	
Male	22 (51.2)	9 (52.9)	13 (50)	
Race				.945
African-American/Black	6 (14.0)	2 (11.8)	3 (11.5)	
Asian	5 (11.6)	2 (11.8)	4 (15.4)	
White	32 (74.4)	13 (76.5)	19 (73.1)	
Cardiac Physiology				
Bi-ventricular	26 (60.5)			
Uni-ventricular	17 (39.5)			
Caregiver Characteristics				
Relationship of Respondent to Child				.318
Biological mother	31 (72.1)	12 (70.6)	19 (73.1)	
Biological father	4 (9.3)	3 (17.6)	1 (3.8)	
Adoptive mother	6 (14)	2 (11.8)	4 (15.4)	
Grandparent	2 (4.6)	0	2 (7.7)	
Gender				
Female	39 (90.7)	14 (82.4)	25 (96.2)	
Male	4 (9.3)	3 (17.6)	1 (3.8)	
Race				.731
African-American/Black	5 (11.6)	2 (11.8)	3 (11.5)	
Asian	1 (2.3)	0	1 (3.8)	
White	36 (81.7)	15 (82.4)	21 (80.8)	
More than 1 race	1 (2.3)	0	1 (3.8)	
	Mean (SD)			
Current age (years)	36.2 (7.7)	33.3 (5.2)	38.1 (8.5)	**.044**[a]

[a] Statistically significant results indicated in **bold**.

Table 2
Summaries of key study variables.[b]

	Sample (N = 43)	Univentricular Physiology (n = 17)	Biventricular Physiology (n = 26)	p-value
	Median (IQR)			
YCPC score	6 (0 – 14)	10 (2, 20)	4 (0, 13)	.086
Morphine milliequivalents[a]				
Total opioid MMEs administered	9.1 (4.5 – 46.4)	29 (12.4, 67)	5.1 (3.5, 13.5)	**.001**
Total non-morphine MMEs administered	5.3 (1.1 – 36.7)	18.8 (5.0, 62.9)	2.25 (0.3, 10.8)	**.003**
Total MME/kg/day administered	0.51 (0.23 – 1.3)	.51 (.24, 1.6)	.50 (.23, .96)	.602
Administered doses of individual opioids[a]	Median (Min, Max)			
Hydromorphone (mg)	0 (0, 36.8)	.17 (0, 36.8)	0 (0, 2.26)	**.008**
Morphine (mg)	3.4 (0, 65.5)	4.3 (0, 65.5)	2 .8 (0, 8.5)	.136
Oxycodone (mg)	1.3 (0, 14)	2 (0, 14)	.7 (0, 4.2)	**.009**
Fentanyl (mcg)	0 (0, 790)	0 (0, 620)	0 (0, 790)	.114

[a] Data reflects opioids administered during ICU stay
[b] Statistically significant results indicated in **bold**.

Discussion

This is the first known study to evaluate relationships between post-operative opioid administration and PTSS in preschool-aged children after cardiac surgery. Other studies have shown favorable relationships between the amount of opioid drugs administered and later development of PTSS or PTSD (Sheridan et al., 2014). Morphine administration, in particular, has been associated with decreased post-traumatic stress (2009). Ours is one of the few known pediatric studies to include multiple opioid drugs as independent variables, rather than focusing exclusively on morphine.

Our data failed to show a favorable reduction in post-traumatic stress with increased total opioid administration. This may be, in part, related to the directionally opposite effect of morphine when compared with non-morphine opioids. Another possible explanation is that children in previous studies were largely healthy before their sudden illness or injury. Our study is one of the first to study relationships between opioid administration and PTSS in young children with underlying illness who, in many cases, would have previously been exposed to opioid medications. Additionally, previous researchers collected longitudinal data compared to the current cross-sectional study. Saxe et al. (2001) reported a correlation between morphine administration and the degree of change in PTSS over a three-to-six-month period. It is not known whether a similar reduction in YCPC scores over time would have been observed among the current sample.

While the relationship was not significant for the total sample, morphine was negatively correlated with YCPC scores in our study. The effect size ($r_s = -.07$) was much smaller when compared to the work presented by Stoddard et al. (2009) who reviewed morphine administration and post-traumatic stress in preschool children after burn injury. Our contrasting findings are likely due to differences in the direction of the effect between groups of children with either single or bi-ventricular cardiac physiology in our study. For single ventricle patients, whose baseline health and pre-operative experiences are presumably different from those with two ventricles, morphine did show a significant, beneficial relationship to YCPC scores ($r_s = -.57$, $p = .017$). There are likely undetermined confounding factors associated with single ventricle physiology which were not considered for the current study. It is unclear whether the patients who received morphine did so under different clinical conditions from those receiving other opioids, or if morphine specifically contributed to a reduction in PTSS. Previous researchers have hypothesized that morphine may reduce hyperarousal symptoms associated with post-traumatic stress due to impaired fear conditioning and reduction in catecholamines, although additional research is needed (Birur et al., 2017; Bryant et al., 2009; Nummenmaa & Tuominen, 2018).

Practice implications

Future research should include longitudinal designs to better understand the relationships between opioid administration (particularly morphine) and post-traumatic stress in preschool children after cardiac surgery. Additional studies are needed to attempt replication of the significant finding between morphine and post-traumatic stress in those with single-ventricle physiology. Studies with larger sample sizes will allow for more robust analysis to evaluate interactions between relevant psychosocial and biological variables, in accordance with Marsac's biopsychosocial framework. Healthcare providers should be attuned to the potential development of PTSS in their preschool-aged patients postoperatively. Anticipatory guidance should be provided to caregivers of these children and appropriate referrals to mental health experts should be initiated when necessary.

Limitations

Although our study was the first of its kind to evaluate the relationship between opioid administration and PTSS in preschool-aged children after cardiac surgery, we acknowledge several limitations. Study

Table 3
Correlations[a] between opioid dosing with subsequent PTSS (N = 43)[c]

Opioid Dosing	YCPC (p-value) N = (43)	YCPC Score (p-value) Univentricular Physiology (n = 17)	YCPC score (p-value) Biventricular Physiology (n = 26)	p-value[b]
Hydromorphone (mg)	.32 (.040)	.32 (.215)	.13 (.523)	.277
Morphine (mg)	−.07 (.643)	−.57 (.017)	.21 (.303)	**.006**
Oxycodone (mg)	.13 (.411)	−.17 (.520)	.18 (.368)	.148
Fentanyl (mcg)	.18 (.262)	−.09 (.726)	.25 (.226)	.154
Total MMEs delivered	.27 (.084)	−.10 (.694)	.25 (.214)	.154
Total non-morphine MMEs delivered	.31 (0.042)	.11 (.669)	.27 (.185)	.312
MME/kg/day	.112 (.455)	.08 (.768)	.15 (.475)	.417

[a] Spearman's *rho* (r_s).
[b] *z*-test of differences between independent correlations.
[c] Statistically significant results indicated in **bold**.

materials were only available in English, decreasing the diversity of the study sample and limiting generalizability of the findings. This was a relatively small study conducted at a single site. Patterns of pain assessment and opioid administration may have been impacted by local culture and staff preferences; replication of these findings in a larger, multi-site study may be warranted. This study could have been further strengthened with a larger sample and multiple points of data collection for YCPC scores. Additionally, prospective determination of pain assessment and documentation with *a priori* opioid administration protocols could help strengthen statistical analysis and interpretation. Potential selection bias existed as participants' willingness to respond to the YCPC may have been influenced by their assessment of the child's mental health at the time of enrollment. Important psychosocial variables, such as parent mental health, parent-child attachment, and parenting support, have previously been associated with post-traumatic stress in early childhood (Feldman et al., 2014; Halevi et al., 2016; Nugent et al., 2006; Owen, 2020) but were not accounted for in the current study. Furthermore, we did not account for potential overlap between PTSS in the context of cardiac surgery and prior trauma exposure except as identified in the YCPC based upon a predetermined list of traumatic events. We also did not address potential overlap between delirium and PTSS. We felt this was an acceptable limitation given the primary aims of the current study. However, we initially hoped to generate future analysis by recording the number of patients who met criteria for delirium according to the Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) and the Preschool Confusion Assessment Method for the ICU (psCAM-ICU) (Paterson et al., 2021; Smith et al., 2016). Only five children in the current study met this criteria for delirium, thereby limiting the ability to generate meaningful statistical analysis. Whether this reflects a low incidence of delirium in this group, incomplete documentation in the medical record, or an insufficient operational definition of "delirium," is unclear.

Conclusion

Preschool-aged children may experience negative psychiatric sequelae, including PTSS or PTSD, after surviving cardiac surgery. Post-traumatic stress is a complex condition with several contributing factors, many of which are poorly understood or difficult to operationalize in early childhood. Pain has been associated with post-traumatic stress in the past; health care professionals must improve our understanding of the most appropriate therapies and mechanisms for pain relief in this vulnerable population, both for the relief of acute postoperative pain and for the alleviation of psychiatric sequelae. Morphine, in particular, appears to have a favorable impact on PTSS in preschool-aged children with single ventricle physiology after cardiac surgery.

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Data sharing statement

Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Kelly Davis at kelly.a.davis@vumc.org.

CRediT authorship contribution statement

Kelly A. Davis: Conceptualization, Methodology, Funding acquisition, Data curation, Validation, Software, Investigation, Writing – original draft. **Mary S. Dietrich:** Validation, Formal analysis, Writing – review & editing. **Mary Jo Gilmer:** Methodology, Writing – review & editing. **D. Catherine Fuchs:** Methodology, Writing – review & editing. **Terrah Foster Akard:** Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

Kelly Davis reports financial support was provided by Vanderbilt Institute for Clinical and Translational Research.

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