Post-traumatic Stress Symptoms in Preschool Children following Cardiac Surgery

By

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Dissertation
Submitted to the Faculty of the
Graduate School of Vanderbilt University
In partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing Science

December 18, 2021

Nashville, Tennessee

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This work is humbly dedicated to small patients who, through no fault of their own, face big battles. Their bravery and resilience are inspiring.

ACKNOWLEDGEMENTS

I gratefully acknowledge Vanderbilt University School of Nursing and the Student Achievement Research Award (SARA) Committee. This work would not have been possible without your financial and institutional support. I would also like to thank the members of my dissertation committee: Dr. Mary Jo Gilmer, Dr. Mary Dietrich, and Dr. Catherine Fuchs. Thank you for gifting me with your unending wisdom, patience, and grace during this process. I am especially grateful to Dr. Terrah Akard, my committee chair and faculty advisor, for your exceptional mentorship and guidance. I am thankful beyond words for your example of scholarship, integrity, leadership, and devotion to your family.

I would like to acknowledge my colleagues in the Division of Pediatric Critical Care at Monroe Carell, Jr. Children's Hospital at Vanderbilt. I am grateful for your endless encouragement as I've walked this journey, and I am in awe of your collective brilliance and dedication to our patients and their families.

To my dear friends and family, who have kept my head above the proverbial water during this and other seasons. "Thank you," seems inadequate, but please know that I deeply appreciate you loving me so well. To the three best nephews in all the land: being your "KK" is one of my greatest joys. I love you to the moon and back.

Finally, but not lastly, I would like to gratefully acknowledge my parents, Don and Christine Davis. Any success I've had reflects your sacrifice, encouragement, and staggering belief in me. Thank you.

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Statement of the Problem

Congenital heart disease (CHD) is the most common birth defect worldwide, with one out of every 100 neonates afflicted by abnormal cardiac anatomy (Chen et al., 2018; van der Linde et al., 2011). There is no cure for CHD, and surgery during infancy or early childhood is often the only option to palliate abnormal intracardiac anatomy. Pediatric cardiac surgery can be a traumatic process which involves both physical and psychiatric stress, pain, and periods of necessary separation of the child from his or her primary parent caregivers.

Children who survive cardiac surgery are at risk to experience post-traumatic stress symptoms (PTSS) and, in some cases, develop post-traumatic stress disorder (PTSD). PTSS may negatively impact the child's neurocognitive development and physical and mental health. Without adequate recognition and treatment, these patients experience unnecessary suffering and decreased quality of life. (A. Kovacs & D. C. Bellinger, 2021; A. H. Kovacs, 2019; Wernovsky & Licht, 2016) In decades past, research has focused extensively on long-term survival for CHD palliation, and surgical outcomes have improved dramatically in recent years (Jacobs et al., 2016; Khairy et al., 2010; van der Linde et al., 2011). While this is reassuring for affected children and their families, the significance of long-term sequelae for these patients, including psychiatric co-morbidities, is amplified throughout their increasingly longer lifespan. (Westhoff-Bleck et al., 2016) As children with CHD grow into adults with complex medical and psychiatric needs, more attention to mental health is needed to foster a healthy transition to adulthood in these patients.

Purpose of the Study

The purpose of this study was to explore relationships among post-traumatic stress in preschool children following cardiac surgery and important clinical and psychosocial variables. Previous research has demonstrated that some children meet criteria for diagnosis of PTSD after a traumatic experience, although many exhibit symptoms below the diagnostic threshold. (McLaughlin et al., 2015) Even in the absence of a PTSD diagnosis, PTSS can cause suffering and functional impairment in affected children (M. S. Scheeringa, Zeanah, Myers, & Putnam, 2005). Therefore, the outcome of interest for this study is the number of PTSS, rather than a clinical diagnosis of PTSD. To develop a holistic understanding of post-traumatic stress in young children after cardiac surgery, there were three primary aims of this study.

Aim 1: Evaluate the relationship between clinical variables and post-traumatic stress symptoms in young children following cardiac surgery. *H1a*: ICU length of stay (LOS) will be positively associated with increased number of PTSS. *H1b:* Total hours of postoperative mechanical ventilation will be positively associated with increased number of PTSS. *H1c:* Children with single ventricle physiology will display higher number of PTSS after cardiac surgery than children with biventricular physiology. *H1d:* Higher number of previous surgical encounters will be positively associated with increased PTSS after cardiac surgery.

Aim 2: Evaluate the relationship between postoperative opioid administration and PTSS in young children following cardiac surgery. _H2a_: Higher doses of opioid administration in the ICU setting will be associated with decreased number of PTSS.

Aim 3: Evaluate the relationship between parental stress and PTSS in young children following cardiac surgery _H3a_: Higher parental stress levels will be associated with an increased number of PTSS in young children following cardiac surgery.

Conceptual Model for the Study

Guided by Marsac's Biopsychosocial Framework of Medical Traumatic Stress (Marsac et al., 2017), which suggests that the development of PTSS in childhood is influenced by biological, psychological, and social variables, the conceptual model for this study is presented in Figure 1 below. Biological and clinical variables assessed in this study included both baseline characteristics of the child's cardiac anatomy and healthcare condition (cardiac physiology, previous surgical experiences), and characteristics associated with the event of cardiac surgery (intensive care unit length of stay, mechanical ventilation, opioid administration). Parental stress is a key component of the child's physical and psychosocial environment and may both impact, and be impacted, by the child's clinical condition. Baseline biological and psychosocial factors may also demonstrate a reciprocating relationship to the child's present cardiac surgical encounter. Ultimately, children may develop post-traumatic stress symptoms following cardiac surgery. We explored the potential relationship between clinical characteristics of the postoperative period, parental stress, and the development of PTSS for preschool children surviving cardiac surgery.

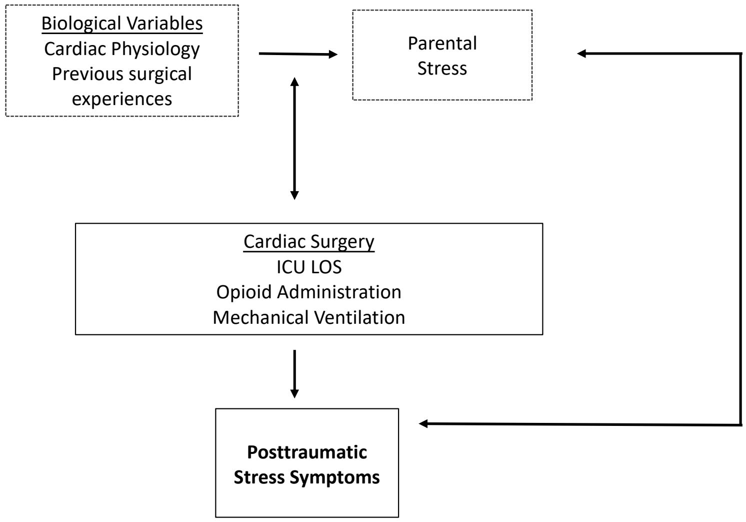

Figure 1. *Conceptual model.*

Scope of the Problem

In the earliest days of CHD palliation, surgical mortality was high and few children survived beyond the first postoperative year (Baum, 2006). Advancements in medical management and surgical techniques have led to improved survival, and approximately 80% of children with CHD will survive to adulthood (Jacobs et al., 2016; Khairy et al., 2010; Pasquali et al., 2020). Given these improved survival outcomes, there is now a greater number of adults than children living with CHD in North America (Khairy et al., 2010).

Improved survival, however, has not necessarily led to reduced morbidity. Many children who require cardiac surgery for CHD will undergo at least one surgical procedure before reaching six years of age. Children who survive cardiac surgery face potential medical, social, and psychiatric challenges. While human adaptation to stress is a normal, protective physiologic mechanism, it is possible to develop disordered stress responses which persist over time. These stress responses may manifest as PTSS or PTSD. Traumatized children with PTSS are at risk for impaired cognitive development (Thomason & Marusak, 2017). This risk is magnified as neurocognitive outcomes are already a concern for children who require cardiac surgery due to the risks associated with cardiopulmonary bypass and the child's baseline physiology (Ilardi et al., 2020; Wernovsky & Licht, 2016; Wernovsky, Shillingford, & Gaynor, 2005).

Relevance to the Field

The prevalence of PTSD in adult patients with CHD (whose own surgical repairs occurred in childhood) is approximately three times higher than the general population; a significant association has been reported between cardiac surgery at an early age in childhood and post-traumatic stress in adulthood (Deng et al., 2016). Unfortunately, there is a lack of research exploring the development of disordered stress responses, including PTSS, in young children post-cardiac surgery. Rather than waiting until adulthood to pursue evaluation and treatment of PTSS, it is critical that we examine the potential development of these symptoms earlier in childhood. Appropriate recognition and intervention in early childhood is necessary to mitigate long-term effects of untreated post-traumatic stress. These long-term effects may include cognitive deficits (Kavanaugh, Dupont-Frechette, Jerskey, & Holler, 2017; Malarbi, Abu-Rayya, Muscara, & Stargatt, 2017), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and chronic inflammation (Agorastos, Pervanidou, Chrousos, & Baker, 2019), and poor cardiovascular health (Pretty, O'Leary, Cairney, & Wade, 2013).

This study described relationships between biological and social components of cardiac surgery in early childhood and the development of PTSS in these patients. The information gleaned from our study provides a valuable first step towards increasing clinician attentiveness to PTSS and identifying patients experiencing these symptoms postoperatively. In the following chapters, details regarding the methodology and results will be discussed based on study aims. Chapter Two describes the relationship between treatment variables relevant to cardiac surgery and PTSS in preschool patients (Aim 1). In Chapter Three, we review data regarding postoperative opioid administration and PTSS in preschool-aged children after cardiac surgery (Aim 2). Chapter Four reviews parenting stress in this unique population and its relationship with PTSS (Aim 3). Finally, we will synthesize the results of the current study in Chapter Five and discuss implications for future research.

Chapter Two

The Relationship between Postoperative Variables and PTSS in Preschool Children after Cardiac Surgery

Submitted for Publication to Pediatrics

Introduction

Congenital heart disease (CHD) is the most common birth defect worldwide, occurring in approximately one percent of all live births, and many affected children will require surgical palliation to survive to adulthood (Bouma & Mulder, 2017). As survival rates for pediatric cardiac surgery continue to improve, there are now more adults than pediatric patients living with CHD (Khan & Gurvitz, 2018; A. H. Kovacs & D. C. Bellinger, 2021; Marelli et al., 2014). Given these trends in survival, long-term sequelae of cardiac disease and necessary medical-surgical interventions are gaining attention in the literature (A. Kovacs, 2019). In particular, psychiatric outcomes are important considerations for the overall morbidity of these patients. Patients with congenital heart disease have demonstrated greater anxiety, depression, and post-traumatic stress disorder (PTSD) when compared with the general population (Deng et al., 2016; Eslami, 2017; Gleason et al., 2019a; Kovacs et al., 2009). Without treatment, these psychiatric conditions may have important implications for patients' quality of life (A. Kovacs, 2019). As children status-post cardiac surgery approach adulthood, their ability to successfully transition into adult CHD (ACHD) programs may be negatively impacted by untreated psychiatric illness. Previous research has demonstrated that PTSD is associated with lower levels of resilience and poor medical compliance in patients who require follow-up care for illness (Jacobsen, 2020; Jersak, Gustin, & Humphrey, 2019).

Debate exists surrounding the legitimacy of PTSD in the context of potentially traumatic medical experiences, although many researchers agree that medical experiences may indeed cause psychiatric trauma for patients. This is particularly true for preschool-aged children who are prone to catastrophizing and lack understanding regarding the necessity of medical interventions (De Young & Landolt, 2018; Drury, Brett, Henry, & Scheeringa, 2013; Pai, Suris, & North, 2017). Furthermore, patients may experience post-traumatic stress symptoms (PTSS) that negatively impact quality of life without meeting the diagnostic threshold for classical PTSD (McLaughlin et al., 2015).

Existing literature shows variability in which aspects of medical treatment may be associated with post-traumatic stress (Indja et al., 2017; Marsac et al., 2017; Meentken, van Beynum, Legerstee, Helbing, & Utens, 2017; Parker et al., 2015). For example, Utens et al. (1998) reported that the number of total surgical procedures experienced by children with CHD was predictive of internalizing and externalizing behavioral problems. More recently, others have reported that treatment experiences such as duration of intensive care unit stay is associated with greater PTSS burden in school-age children (Connolly, McClowry, Hayman, Mahony, & Artman, 2004). Although many patients with CHD require surgery in their infancy or preschool years, gaps exist in research focusing on post-traumatic stress after cardiac surgery in this age group.

Improving the understanding of PTSS in preschool-aged children after cardiac surgery may help guide screening and initiation of referrals by members of the healthcare team who provide postoperative care to these patients. Thus, the purpose of this study was to explore relationships among treatment variables associated with pediatric cardiac surgery and post-traumatic stress in early childhood. Co-variates of interest included a) cardiac physiology (uni- or bi-ventricular physiology), b) number of previous surgeries experienced by the child, c) length of postoperative stay in the intensive care unit, and d) duration of mechanical ventilation. We hypothesized that single ventricle physiology, higher number of previous surgeries, longer ICU stay, and longer duration of mechanical ventilation would be associated with increased symptoms of post-traumatic stress.

Methods

This study was part of a larger project examining biopsychosocial aspects of post-traumatic stress symptoms in preschool children after cardiac surgery. Our work was guided by Marsac's Biopsychosocial Framework of Medical Traumatic Stress, which highlights biological, psychological, and social risk factors that may contribute to the development of post-traumatic stress in children undergoing medical treatment. (Marsac, Kassam-Adams, Delahanty, Widaman, & Barakat, 2014)

After approval by the Institutional Review Board, caregivers were recruited to participate in a cross-sectional, descriptive study using surveys and medical chart review. Eligible caregivers, including biological mothers or fathers, adoptive parents, step-parents, or legal guardians, were identified via a review of the surgical caseload at our institution over the previous two years. To be considered eligible, caregivers were at least 18 years of age, able to speak and understand English, and had living children between three years and six years of age at study onset who had undergone cardiac surgery at our institution within the preceding two years. Parents or caregivers of children who received interventional procedures only (i.e., cardiac catheterizations or electrophysiology studies) were excluded. We solicited responses from the child's primary caregiver, defined as the caregiver spending the greatest number of waking hours with the child each week.

Data collection occurred during an 11-week period from September to December 2020. Introductory letters describing the study were distributed via US Mail to potential participants. Contact information was provided for caregivers who wished to opt-out of further communication regarding the study. Within 7-10 days of mailing letters, the first author attempted to contact potential participants via telephone to provide additional details about the study and begin the enrollment process. Initially, 117 eligible caregivers were identified and fifty-three were successfully contacted. Of those, 44 (83%) participated in the study.

Participants completed consent documentation, demographic information forms, and the Young Child PTSD Checklist (YCPC) electronically via REDCap. REDCap is a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2019; Harris et al., 2009). Physical copies of the consent document and study materials were made available to participants, although all elected to participate electronically. Those who completed all study measures received a retail gift card as reimbursement for their time and participation.

The 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 is an abbreviated format of the PTSD module of the

Diagnostic Infant and Preschool Assessment (DIPA), which was been successfully used elsewhere in early childhood mental health research. Updated for DSM-V, the YCPC contains 42 items with Likert values that are summed for an overall score. The YCPC has demonstrated strong psychometric properties in the literature, with good internal consistency (α = .77) and concurrent criterion validity when compared to the PTSD module of the DIPA (Haag & Landolt, 2017; M. Scheeringa, 2020). Internal consistency of the measure was excellent in this study, with Cronbach's α = 0.94.

The principal investigator (PI) retrieved treatment data from the electronic medical record. Those variables included child demographics at time of surgery and clinical characteristics such as baseline cardiac physiology, medical-surgical history, and details of the child's postoperative clinical course in accordance with the aims of the study.

Statistical analysis

Statistical analyses were performed using IBM SPSS (26). Descriptive statistics were generated for each study variable; nominal data is represented by frequency counts and continuous data is represented by means and standard deviations or medians and quartile ranges as appropriate. We used student's *t*-test, Mann-Whitney U, and Chi-squared testing to observe between-group differences for normally distributed data, non-parametric continuous data, and categorical data, respectively. Measures of association were generated between each of the independent co-variables and the outcome variable (YCPC score) for this study.

Results

Of the 44 enrolled participants, one child did not require postoperative ICU admission and the associated data was therefore excluded from the analyses. Characteristics of the remaining 43 participants are presented in Table 1. Seventeen (39.5%) of the children had single ventricle cardiac physiology. Approximately half of the children were male (n = 22, 51.2%), and most of the caregivers (n = 39, 90.7%) were female. Children were a median age of 40.4 months at the time of surgery and 55.2 months of age at the time of data collection. As also shown in Table 1, children with single ventricle physiology were significantly older at the time of surgery than those with biventricular physiology (median 45.5 vs. 29.2 months respectively, p = .007) and caregivers of single ventricle patients were younger (mean: 33 vs. 38 years respectively, p = .044) than caregivers of children with biventricular physiology. No other statistically significant differences in demographic characteristics were observed between the two groups.

The median YCPC score for the total sample was 6.0 (IQR=0,14). Five participants (11.6%) scored 26 or higher on the YCPC, which is the threshold for presumed clinical diagnosis of PTSD. While the difference was not statistically significant, scores for the single ventricle group tended to be considerably higher than those for the biventricular group (median = 10.0 vs. 4.0 respectively, p = .086). Summaries of postoperative treatment variables and YCPC scores are displayed in Table 2. While none of the correlations of age and treatment variables achieved the criteria for statistical significance (p > .05), the strongest correlations were observed for age (r_s = 0.30), total ICU length of stay (r_s = 0.25), and number of prior surgeries (r_s =

0.23, applicable to single ventricle physiology only, n=17). Given the very different treatment experiences apparent for the two groups of children with single ventricle versus biventricular physiology, we generated and compared correlations of those treatment experiences with YCPC scores. As shown in Table 3, differing patterns of association were observed in the two groups. The correlation of ICU LOS with YCPC scores was inverse in the single ventricle group while equally strong, but in the positive direction in the bi-ventricular group ($r_s \sim \pm 0.30$) with that difference being statistically significant (p = .034). A similar pattern of difference, although not as extreme, was observed for duration of mechanical ventilation (p = .094, see Table 3).

Discussion

Despite extensive research focused on neurodevelopmental and psychosocial outcomes in patients with CHD, few studies have examined PTSS (Asschenfeldt et al., 2020; Brosig et al., 2017; Chun Yee So, Ho Cheung Li, & Yan Ho, 2019; Goldberg et al., 2019; Ilardi et al., 2020; Sanz et al., 2018). Additionally, research evaluating PTSS after cardiac surgery typically excludes preschool-aged children. Our study was one of the first to evaluate post-traumatic stress following cardiac surgery in this age group (Connolly et al., 2004; Toren & Horesh, 2007).

Our study did not show a significant relationship between ICU LOS and PTSS in this sample of preschoolers after cardiac surgery, contrary to previous reports in school-age children (Connolly et al., 2004). Previous studies have demonstrated significant relationships between number of surgical encounters and worse psychosocial outcomes, including anxiety, behavioral disorders, and decreased quality of life, although these studies were conducted in school-age children (Dulfer et al., 2016). The data from our work with preschool children did not support a similar correlation with post-traumatic stress. Duration of mechanical ventilation was also not significantly correlated with PTSS.

The small effect sizes in our data were likely impacted by directionally opposite effects noted between groups of children with differing underlying physiology. Interestingly, duration of mechanical ventilation appeared to show a moderate, albeit not significant, effect on PTSS for children with single ventricle physiology. Children in this age group often require sedative medications to protect indwelling medical devices and it is possible that the child's level of postoperative sedation influenced the development of PTSS. Additional research is needed to corroborate this finding.

A small-moderate effect size approaching significance was noted between age at surgery and YCPC scores. While this was not one of our originally intended variables, age was analyzed independently due to the significant difference in age between children with single- and bi-ventricular physiology. Our study showed an association between older age at time of surgery and PTSS. Children in this study were between three and six years at the time of data collection, and could have been as young as one year of age at the time of their surgery. Given the memory processing and consolidation inherent to development of PTSS, it is possible that a) younger children in this sample were protected from the development of PTSS due to immature memory consolidation or b) parents of younger children in our sample did not recognize their child's behavioral or verbal expression as PTSS (Cordón, Pipe, Sayfan, Melinder, & Goodman, 2004; De Young, Kenardy, & Cobham, 2011b). Other studies regarding preschool trauma have not shown an association between age and greater burden of

PTSS, although this is the first known study to specifically investigate children in this age group after cardiac surgery (Schechter et al., 2017).

Limitations

There are several limitations to consider. First, this is a small, single-center study with a few significant outliers; a larger sample size would be helpful to evaluate possible relationships. The sample was limited to English-speaking participants only and replication in larger, more diverse samples is warranted to improve generalizability. This is a cross-sectional study and, as such, is subject to methodological challenges as we did not collect baseline data. For children who experienced prior surgeries, it is unknown whether caregivers would have reported similar YCPC scores prior to the most recent surgical event. Prospective data collection to assess baseline post-traumatic stress and change after new surgical encounters may be warranted. Our study may further be limited by potential selection bias, as participants' willingness to respond to the YCPC may have been influenced by their perception of the child's mental health at the time of enrollment.

Clinical Implications for Practice

Some of the findings in this study were discrepant with similar studies conducted with school age children. Further examination in larger studies with preschool age children will be meaningful to identify potential relationships between PTSS and treatment variables to identify key opportunities for future intervention development and testing. Additional research is needed to further our understanding of these relationships and guide screening for preschool patients who may be most vulnerable to post-traumatic stress postoperatively. Health care providers of preschool patients with

CHD should anticipate the potential development of PTSS in the postoperative setting, and initiate in-depth screenings, assessments, and referrals to mental health professionals as indicated.

Funding Statement
Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University Medical Center. Research support was provided by the Vanderbilt Institute for Clinical and Translational Research (UL1 TR000445 NCATS/NIH) and Vanderbilt University School of Nursing Student Achievement Research Award.

Acknowledgement
We thank the parents and caregivers who participated in this study. We gratefully acknowledge Dr. David Bichell, Chief, Pediatric Cardiac Surgery at Monroe Carell, Jr. Children's Hospital at Vanderbilt for his assistance with this project

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
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)	
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				.128
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

Table 2. Summary statistics for Key Study Variables				
Variable	**Total Sample (N = 43)**	**Single Ventricle Physiology (N = 17)**	**Bi-ventricular physiology (N = 26)**	**p-value***
	Median (IQR)			
Number of previous surgeries	1 (0, 3)	3 (2, 4)	0 (0, 1)	< .001
Length of stay (days)	2 (1, 4)	5 (2, 9)	1 (1, 2)	< .001
Duration of mechanical ventilation (hours)	13.8 (4.8, 27.5)	27.5 (14.8, 41.5)	6.8 (4.23, 14.7)	< .001
YCPC Score	6 (0, 14)	10 (2, 20)	4 (0, 13)	.086
*Mann-Whitney U				

Table 3. Relationships of demographics and treatment variables with YCPC scores.				
	YCPC Scores[a]			**p-value[b]**
Variable	**Total Sample (N = 43)**	**Single Ventricle Physiology (N = 17)**	**Bi-ventricular physiology (N = 26)**	
Age at surgery	.30 (.052)	.14 (.585)	.32 (.109)	.288
Number of prior surgeries	.23 (.135)	.11 (.669)	---	---
Duration of Intubation (hours)	.12 (.435)	-.38 (.136)	.05 (.792)	.094
ICU Length of study (days)	.25 (.114)	-.29 (.253)	.30 (.131)	.034
[a] r_s (p-value) [b] Test of between-group differences for correlations between treatment variables and YCPC scores				

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Chapter Three

The Relationship between Postoperative Opioid Administration and PTSS in Preschool Children after Cardiac Surgery

Submitted for publication to Journal of Pediatric Nursing

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, Santacrose, Farnsworth, & MacDougall, 2019; Kassam-Adams, Garcia-España, Fein, & Winston, 2005; Meentken et al., 2017). Researchers have investigated contributing factors to the development of post-traumatic stress to identify patients who are most vulnerable to PTSD. Pain has been associated with PTSD in both pediatric and adult patients (Archer et al., 2016; Gold, Kant, & Kim, 2008; Norman, Stein, Dimsdale, & Hoyt, 2008; Ravn, Hartvigsen, Hansen, Sterling, & Andersen, 2018). Previous research 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 (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010; Saxe et al., 2001; Stoddard et al., 2009). 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 post-traumatic stress symptoms (PTSS) even in the absence of a clinical diagnosis (De Young & Landolt, 2018; Gigengack, van Meijel, Alisic, & Lindauer, 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 post-traumatic stress symptoms (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, Kenardy, & Cobham, 2011a; De Young et al., 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. 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, Ford, & Briggs-Gowan, 2013; Van der Kolk, 2015). These risks are particularly problematic for children who require cardiac surgery (Cassidy et al., 2018; Deng et al., 2016; Gleason et al., 2019a; 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, Borzadaran, Zamani, & Shabani, 2020; Ravn et al., 2018; Stahlschmidt, Rosenkranz, Dobe, & Wager, 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.

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, Harvey, Guthrie, & Moulds, 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. Relationships between opioid administration and PTSS have been variable in the literature. 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, Hamiel, Pardo-Aviv, & Laor, 2017).

Conceptual Framework

This study was part of a larger project examining potential biological, psychological, and social contributors to post-traumatic stress symptoms in preschool children after cardiac surgery. The conceptual framework (see Figure 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 experiences or events (Marsac et al., 2014). Opioid administration is a modifiable variable related to the surgical event.

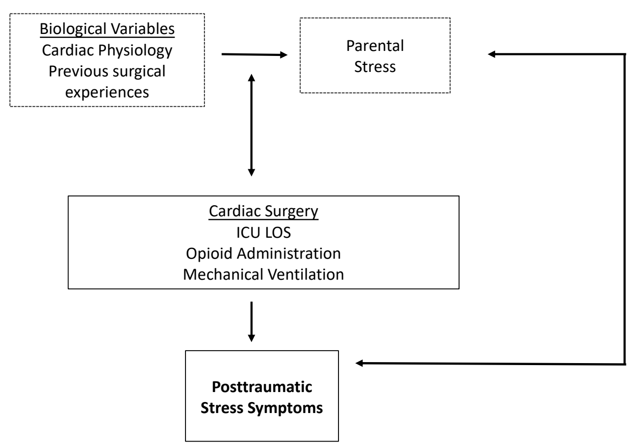

Figure 1. *Conceptual model.*

Methods

Sample

Institutional Review Board approval was obtained prior to the study. We reviewed our institution's surgical caseload from 2018-2020 to screen for eligible participants. 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.

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 principal investigator 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 (α = .77) and concurrent criterion validity when compared to the PTSD module of the DIPA (Haag & Landolt, 2017; M. Scheeringa, 2020). The internal consistency of the scores in this study was considerably higher with a Cronbach's α = 0.94.

Opioid administration: The principal investigator 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 (2001) and Stoddard (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., 2019; Harris et al., 2009). 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 used 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.

Summaries of the opioid administrations and YCPC scores are presented in Table 2. 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 (MS. 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). As children with single ventricle physiology generally have different healthcare experiences than children with two cardiac ventricles, 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 (ρ = -.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).

Discussion

This is the first known study to evaluate relationships between postoperative 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 (Stoddard et al., 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 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, Moore, & Davis, 2017; Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009; Nummenmaa & Tuominen, 2018).

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 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 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, Vengrober, & Ebstein, 2014; Halevi, Djalovski, Vengrober, & Feldman, 2016; Nugent, Ostrowski, Christopher, & Delahanty, 2006; Owen, 2020) but were not accounted for in the current study.

Implications for practice and research

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 would also allow for more robust analysis to include relevant psychosocial variables. 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.

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.

Funding Statement
Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University Medical Center. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Research support was provided by the Vanderbilt Institute for Clinical and Translational Research (UL1 TR000445 NCATS/NIH) and by the Vanderbilt University School of Nursing Student Achievement Research Award.

Acknowledgement
We thank the parents and caregivers who participated in this study. We gratefully acknowledge Dr. David Bichell, Chief, Pediatric Cardiac Surgery at Monroe Carell Jr. Children’s Hospital at Vanderbilt for his assistance with this project.

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
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

Table 2. Summaries of key study variables.				
	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

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

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Chapter Four

Associations between Parenting Stress and Child PTSS in Preschool Children after Cardiac Surgery

Submitted for publication to Journal of Child and Family Studies

Introduction

Congenital heart disease (CHD) is the most common birth defect worldwide, with approximately one out of every 100 neonates afflicted with abnormal cardiac anatomy (Bouma & Mulder, 2017; van der Linde et al., 2011). Severity of heart disease varies widely, ranging from minor defects to complex malformations requiring multiple surgical interventions. Survival rates for pediatric patients undergoing cardiac surgery have dramatically improved in recent decades (Bouma & Mulder, 2017; Triedman & Newburger, 2016). Long-term comorbidities, including non-cardiac sequelae, of CHD and necessary medical-surgical interventions have become an international research priority in light of improved patient survival (Cassidy et al., 2018; Deng et al., 2016; Gleason et al., 2019b; Ilardi et al., 2020; A. Kovacs & D. C. Bellinger, 2021; Marino et al., 2012; Meentken et al., 2017; Wernovsky & Licht, 2016).

Neurocognitive and mental health outcomes in both CHD-affected children and their parents are of particular interest to clinicians and researchers (Sood, Jacobs, & Marino, 2021). Available literature suggests that school-aged children, adolescents, and adults with CHD, many of whom required cardiac surgery, are more likely than healthy controls to experience post-traumatic stress disorder (PTSD), depression, anxiety, and other negative psychiatric outcomes (Deng et al., 2016; Gonzalez et al., 2021; Kovacs & Utens, 2015). Although an estimated 40,000 American children require cardiac surgery each year (Jacobs et al., 2016), gaps remain for research describing mental health outcomes in children following cardiac surgery, particularly for preschool-aged children.

Most pediatric researchers agree that medical experiences, such as cardiac surgery, may cause psychiatric trauma for young patients (Forgey & Bursch, 2013). Preschool-aged children who lack understanding of the necessity of medical interventions may catastrophize even relatively minor procedures (De Young & Landolt, 2018; Drury et al., 2013; Pai et al., 2017). In some cases, these traumatic experiences will contribute to the development of PTSD. Diagnosing PTSD in young children has historically been difficult because of conceptual ambiguity, disagreement over diagnostic criteria, and limitations in assessment of the pre-verbal child (De Young & Landolt, 2018; Gigengack et al., 2015; Simonelli, 2013). Even without a clinical diagnosis of PTSD, however, some preschool-aged patients may exhibit post-traumatic stress symptoms (PTSS) after cardiac surgery (McLaughlin et al., 2015). In the absence of a clinical diagnosis, PTSS may be underappreciated by caregivers and healthcare providers, leading to gaps in mental health referrals and follow-up care. Children who exhibit PTSS may be at risk for decreased quality of life and delays in neurocognitive development (Grasso et al., 2013; Van der Kolk, 2015). Young children less than six years of age are particularly susceptible to the sequelae of untreated traumatic stress in the context of rapid brain growth and cellular differentiation inherent to early childhood (Grasso et al., 2013).

The literature suggests that a child's congenital heart disease and associated treatment may also have a negative impact on parental mental health, as parents of children with CHD may themselves suffer from post-traumatic stress (Kaugars, Shields, & Brosig, 2018; Lawoko & Soares, 2002; McClung, Glidewell, & Farr, 2018; Menahem, Poulakis, & Prior, 2008; Wray et al., 2018). Previous studies have demonstrated positive correlations between parental PTSD and child PTSS (Salloum, Smith Stover, Swaidan, & Storch, 2015). In fact, parental distress and psychopathology have been more commonly associated with child PTSS than individual or treatment-related variables following medical experiences, particularly in younger children (Dow, Kendardy, Long, & Le Brocque, 2012; Schechter et al., 2017; M. Scheeringa, Myers, Putnam, & Zeanah, 2015). Despite the well-documented associations between parental psychopathology and child PTSS in young children outside of the CHD population, this relationship has yet to be explored in young children following cardiac surgery. The purpose of this study was to determine the relationship between parental stress and early childhood post-traumatic stress following cardiac surgery. We hypothesized that greater parental stress would be positively correlated with post-traumatic stress symptoms in preschool children after cardiac surgery.

Methods

Participants

After Institutional Review Board approval, we recruited caregivers to participate in a cross-sectional study using surveys and medical chart reviews. We identified potential participants via review of the surgical caseload at our institution over the previous two years. Eligible caregivers (biological mothers/fathers, adoptive parents, stepparents, and legal guardians) (a) had living children between three and six years of age at study onset with cardiac surgery occurring in the two previous years, (b) spoke and understood English, and (c) were at least 18 years of age. Exclusion criteria included parents or caregivers of children who received interventional procedures only (i.e., cardiac catheterizations or electrophysiology studies). When more than one caregiver was available for each child, we included the primary caregiver, defined as the individual who was in direct contact with the child for the greatest number of waking hours per week.

Procedures

Data collection occurred over 11-weeks from September to December 2020. The principal investigator (PI) mailed introductory letters describing the study to potential participants. Parents could opt-out via a phone number or email address provided in the letter. Within 10 days of mailing letters, the PI called potential participants to describe the study, confirm eligibility, and answer questions. Interested participants provided verbal and written consent. All participants signed consent documents via REDCap, a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2019; Harris et al., 2009). After documentation of informed consent, the PI emailed participants a RedCap link to complete study measures. Participants received email reminders every 48 hours (up to five occurrences) until measures were complete. Participants received $50 electronic gift cards as a reimbursement for participation.

Measures

Demographic Characteristics

Participants completed demographic questionnaires related to parent, child, and home environment characteristics. The PI conducted a medical chart review to document child age and underlying cardiac physiology.

Post-traumatic stress symptoms

Parents completed the 42-item Young Child PTSD Checklist (YCPC) (Meentken et al., 2017; Meentken et al., 2020; MS. Scheeringa, 2014; M. S. Scheeringa et al., 2005) to assess PTSS in children between one and six years of age. It is an abbreviated form of the PTSD module of Scheeringa's (2014) Diagnostic Infant and Preschool Assessment (DIPA), which was successfully used by the PI in preliminary work. Possible scores on the YCPC range from 0 to 92. The YCPC has demonstrated strong psychometric properties with good internal consistency ($\alpha = .77$) and concurrent criterion validity when compared to the PTSD module of the DIPA (Haag & Landolt, 2017; M. Scheeringa, 2020). The internal consistency of the scores in this study was 0.94.

Parenting Stress

Parents completed the 15-item short-form version of the Pediatric Inventory for Parents (PIP) to assess parental stress related to parenting a child with chronic illness (Casaña-Granell et al., 2018; Larson, Latendresse, Teasdale, & Limbers, 2020; Vrijmoet-Wiersma et al., 2010). We added one item (#37: "talking to family members about my child's illness") from the original long-version PIP (R Streisand, Braniecki, Tercyak, & Kazak, 2001), yielding a total of 16 unique items. This addition was based on our preliminary work where mothers of children surviving cardiac surgery expressed concern about communication with family members who did not understand their child's condition. Caregivers rated the frequency and level of difficulty for each item according to five-point Likert responses. Individual item responses were combined to produce Frequency (PIP-F) and Difficulty (PIP-D) subscale scores that ranged from 0 to 80. Strong internal consistency (Cronbach's α = .80 - .96) has been reported among both the original version and subsequent translations and short-forms (Casaña-Granell et al., 2018; R Streisand et al., 2001; Vrijmoet-Wiersma et al., 2010). Positive correlations between total PIP scores and anxiety measures in parents support the construct validity of this instrument (R Streisand et al., 2001). Internal consistency scores were excellent in our sample, with Cronbach's α = 0.93 for the PIP-F and 0.93 for the PIP-D scores.

Analysis

Statistical analyses were performed using IBM SPSS (26). Descriptive statistics were generated for each study variable; nominal data were summarized by frequency counts and continuous data by means and standard deviations or medians and quartile ranges as appropriate. We used student's *t*-test, Mann-Whitney U, and Chi-squared testing to observe between-group differences for normally distributed data, non-parametric continuous data, and categorical data, respectively. As appropriate, we used Pearson and Spearman correlations to assess associations of demographic characteristics with the two stress measures (PIP-F, PIP-D) and with the child YCPC scores. After data transformation (square root of parental age, log of YCPC scores), we generated of the strength of the association between PIP scores and the outcome variable (YCPC score) using linear regression. Statistical significance was determined by $p < .05$.

Results

One hundred and seventeen eligible caregivers were identified, and we successfully contacted 53. Of those, 44 (83%) participated in the study. Most caregivers were female (n = 39, 90.7%) and biological mothers (n = 31, 72.1%). Caregivers of single ventricle patients were younger (mean: 33 vs. 38 years respectively, $p = .044$) than caregivers of children with biventricular physiology. No other statistically significant differences in demographic characteristics were observed between the two groups of caregivers. Full details of parent caregiver demographic characteristics are in Table 1. Approximately half of the children were male (n = 22, 51.2%). Children were a median age of 40.4 months at the time of surgery. 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 those with biventricular physiology (median 45.5 vs. 29.2 months respectively, $p = .007$). Table 2 contains detailed child demographic and clinical data.

Summaries of YCPC scores and PIP scores are presented in Table 3. The median YCPC score for the total sample was 6.0 (IQR 0,14). Five children (11.6%) received scores of 26 or higher on the YCPC, which is the threshold for presumed clinical diagnosis of PTSD (MS. Scheeringa, 2014). Scores for the single ventricle group were higher than those for the biventricular group (median = 10.0 vs. 4.0 respectively, $p = .086$). While the differences were not statistically significant, caregivers of children with single ventricle physiology tended to report higher levels of stress than caregivers of children with bi-ventricular physiology.

A statistically significant correlation resulted between the two PIP subscales (*r* = .38, p = .011); however, almost all of that correlation was within the group of caregivers of children with biventricular physiology (*r* = .54, p = .005 vs. single ventricle: *r* = .38, p = -.09, p = .730). Univariate and multivariate correlations of the PIP scores with the YCPC scores are found in Table 4. None of the correlations achieved the level of statistical significance; however, several patterns for further investigation became apparent. In general, the strength of the correlation of the PIP-F scores with the YCPC scores was substantially larger than that respective correlation for the PIP-D scores. This effect was apparent in the overall sample (*r* = .29, p = .058 vs. *r* = .19, p = .232), yet the difference was magnified within the group of single ventricle caregivers (*r* = .42, p = .094 vs. *r* = .18, p = .184). Again, while not statistically significant, this pattern of differential strength remained in the multivariate analysis within the single ventricle group (*r* = .44, p = .084 vs. *r* = .22, p = .360) (Table 4). Post-hoc correlations of demographic characteristics with the YCPC scores were conducted. Only a statistically significant inverse correlation with age of the caregiver was observed (*r* = -.32, p = .035). Including caregiver age as a covariate in the tests of the correlations between PIP and YCPC scores revealed no meaningful differences in the size of those effects.

Discussion

This study was one of the first to examine the relationship between illness-related parenting stress and PTSS in preschool children after cardiac surgery. The focus on post-traumatic stress in this population, rather than other mental health outcomes such as anxiety and depression, represents a novel contribution to the literature (Gleason et al., 2019b). In contrast to existing literature, results do not suggest a statistically significant relationship between parental stress according to PIP scores and PTSS in preschool children surviving cardiac surgery. While the results were not statistically significant, the difference in median PIP-F and PIP-D scores for caregivers of children with differing cardiac physiology was consistent with existing literature. Unique patterns of parenting stress in caregivers of children with single ventricle physiology have been well-described (Golfenshtein, Hanlon, Deatrick, & Medoff-Cooper, 2019).

Younger parents reported significantly higher levels of stress according to PIP-D scores. This is similar to previous literature for caregivers of children with cancer (R Streisand et al., 2001) and inflammatory bowel disease (Guilfoyle, Denson, Baldassano, & Hommel, 2012), although not with diabetes (R. Streisand, Swift, Wickmark, Chen, & Holmes, 2005). Children of younger caregivers did have significantly higher YCPC scores (Table 5). Previous research has explored the relationship between child PTSS and parenting factors such as parent gender, mental health, or parenting style; to our knowledge, none of the existing literature has examined the correlation between parental age and child PTSS (Wise & Delahanty, 2017).

Interestingly, PIP-D scores were not related to household income, although our data showed a significant correlation between household income and PIP-F scores. This suggests that external resources may impact the frequency, but not the degree, of stress experienced by parents of preschool children requiring cardiac surgery. For example, those with fewer financial resources may more frequently experience stressors such as uncertainty about the family’s future (Vrijmoet-Wiersma et al., 2010), although this uncertainty may be similarly difficult for caregivers regardless of income. It is also possible that caregivers' lower income levels may reflect the frequency with which they experience stressful events related to their child's illness and cardiac surgery.

Our data did not yield significant relationships between PIP and YCPC scores. We did note stronger, though not significant, patterns of association between PIP and YCPC scores in caregivers of children with single ventricle physiology. This contrasts with the biventricular physiology group, where YCPC scores reported by caregivers were only weakly associated with PIP scores. The discordance between groups of caregivers whose children had different cardiac physiology likely contributed to the modest effect sizes seen in our overall sample. We anticipate that the difference in these correlations is influenced by the unique medical and surgical experiences of children with single ventricle physiology and the subsequent demands on their family (Goldberg et al., 2019; Golfenshtein et al., 2019). Our associations between parental stress scores and child PTSS were not as large as those reported by Salloum et al. (2015), although children in that study were older than our sample and experienced interpersonal, rather than medically-related, trauma. Multivariate analyses including caregiver age and income levels did not alter the significance of our initial results.

Clinical Implications

Our study supports the growing attention to mental health research in children with CHD who survive surgical palliation (Gonzalez et al., 2021; Marino et al., 2012; Sood et al., 2021). Clinicians caring for preschool-aged patients requiring cardiac surgery must be attuned to the potential development of post-traumatic stress and should initiate referrals to mental health professionals when appropriate. Based on our data, clinicians should be attentive to caregivers who may experience increased stress, particularly for those who are younger or have limited financial resources.

Limitations and Future Directions

We acknowledge that our study may be limited by potential selection bias, as participants' willingness to respond to the YCPC may have been influenced by their perception of the child's mental health at the time of enrollment. This is a small, single-center study and a larger, more diverse sample size would allow for more robust statistical analysis. The sample was limited to English-speaking participants who were primarily female; replication in larger, more diverse samples is warranted to improve generalizability. Our study focused exclusively on parenting stress related to the care of a child with a chronic illness and did not take other sources of stress into consideration. In particular, our study did not measure parental post-traumatic stress, which has been associated with child PTSS in the literature (Cervin, Salloum, Ruth, & Storch, 2020). Future studies should consider parental PTSD and other potential covariables to identify patients most in need of referrals for specialty mental health care and for targeted intervention development. Given the differences noted between both children and parents faced with single- versus bi-ventricular physiology, future studies should consider these parent-child dyads separately. Longitudinal studies are warranted to explore the trajectory of PTSS in this population and the relationship to long-term neurocognitive outcomes.

Conclusion

Our study provides insight to post-traumatic stress symptoms seen in preschool-aged children after cardiac surgery. Contrary to our hypothesis, parenting stress scores according to the PIP-SF were not associated with child PTSS, although interesting differences were revealed between groups of children with single- versus bi-ventricular physiology. In our study, younger caregiver age was associated with higher burden of child PTSS. More research is critical to better understand risk factors for the development and expression of PTSS in young children following cardiac surgery, and to provide targeted intervention and support for these vulnerable children and their families.

Table 1. Summaries of caregiver characteristics (N = 43)				
Variable	**Sample (N = 43)**	**Univentricular Physiology (N = 17)**	**Biventricular Physiology (N = 26)**	**p-value[a]**
		Mean (SD)		
Current age (years)	36.2 (7.7)	33.3 (5.2)	38.1 (8.5)	.044
		N (%)		
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				.128
Female	39 (90.7)	14 (82.4)	25 (96.2)	
Male	4 (9.3)	3 (17.6)	1 (3.8)	
Race[b]				.731
African-American/Black	5 (11.6)	2 (11.8)	3 (11.5)	
Asian	1 (2.3)	0	1 (3.8)	
White	35 (81.4)	14 (82.4)	21 (80.8)	
More than 1 race	1 (2.3)	0	1 (3.8)	
Prenatal Diagnosis of CHD				.001
Prenatal CHD diagnosis	17	12	5	
Postnatal CHD diagnosis	26	5	21	
Household Income				.068
< $10,000	1 (2.3)	1 (5.9)	0	
$10,000 – 50,999	16 (37.2)	9 (52.9)	7 (26.9)	
$51 – 99,999	16 (37.2)	4 (23.5)	12 (46.2)	
$100,000 or more	10 (23.3)	3 (17.6)	7 (26.9)	
Caregiver works outside the home				.234
Yes	25 (58.1)	8 (47.1)	17 (65.4)	
No	18 (41.9)	9 (52.9)	9 (34.6)	
Education				.076
Some high school	2 (4.7)	1 (5.9)	1 (3.8)	
Completed high school	8 (18.6)	3 (17.6)	5 (19.2)	
Some college	12 (27.9)	4 (23.5)	8 (30.8)	
Completed college	14 (32.6)	9 (52.9)	5 (19.2)	
Advanced degree	7 (16.3)	0	7 (26.9)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
Number of people living in home	4 (44,5)		4 (4, 5.3)	.505
Number of children	2 (2,3)		2 (2,3)	.752

[a] Test of between-group differences (Chi-Square Test for categorical; t-test or Mann-Whitney test for continuous)
[b] Missing data = 1; N = 42

Table 2. Summary of Child Characteristics (N = 43)				
	Sample (N = 43)	**Univentricular Physiology (N = 17)**	**Biventricular Physiology (N = 26)**	**p-value[b]**
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
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)	
[b] Test of between-group differences				

Table 3. Summaries of key study variables				
	Sample (N = 43)	**Univentricular Physiology (N = 17)**	**Biventricular Physiology (N = 26)**	**p-value[b]**
	Median (IQR)			
YCPC Score	6 (0, 14)	10 (2, 20)	4 (0, 13)	.086
	Mean (SD)			
PIP-F	38.5 (15.3)	41.8 (15.8)	36.3 (14.9)	.258
PIP-D	40.7 (15.9)	45.2 (8.8)	37.8 (17.4)	.073
[b] Test of between-group differences for YCPC (Mann-Whitney), PIP-F, and PIP-D (independent *t*–test) scores				

Table 4. Bivariate and multivariate associations of PIP scores with YCPC scores.				
	Overall Sample (N=43)			
Variable	**Bivariate**	**p-value**	**Multivariate**	**p-value**
PIP-F	.29	.058	.26	.122
PIP-D	.19	.232	.09	.596
Multiple R			.30	.148
Single Ventricle Physiology (N = 17)				
Variable	**Bivariate**	**p-value**	**Multivariate**	**p-value**
PIP-F	.42	.094	.44	.084
PIP-D	.18	.184	.22	.360
Multiple R			.47	.167
Bi-ventricular physiology (N = 26)				
Variable	**Bivariate**	**p-value**	**Multivariate**	**p-value**
PIP-F	.15	.460	.12	.622
PIP-D	.12	.557	.06	.823
Multiple R			.16	.746

Note: YCPC scores log-transformed to normal for linear regressions

Table 5. Correlations of caregiver characteristics with PIP and YCPC scores (N = 43)			
Variable	**PIP-F**	**PIP-D**	**YCPC**
Caregiver age[a]	-.23 (.144)	-.37 (.015)	-.32 (.035)
Caregiver gender[a]	-.09 (.586)	.19 (.212)	.13 (.404)
Caregiver education[b]	-.12 (.429)	.09 (.587)	.07 (.639)
Income[b]	-.35 (.022)	-.17 (.286)	-.06 (.682)
Caregiver race[a,]	-.10 (.545)	-.26 (.102)	.01 (.963)

[a]Pearson's or point-biserial *r* (p-value)
[b]r_s (p-value)
Note: Caregiver gender: '1' Male, '2' Female; Caregiver race: '0' Non-white, '1' White

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Chapter Five

Conclusion

This was the first known study to explore post-traumatic stress symptoms exclusively in preschool-aged children after cardiac surgery. Results support the premise that preschool-aged children may suffer from PTSS postoperatively. Our work provides an important first step to understanding biopsychosocial factors as they relate to the development of PTSS in this population. Furthermore, our work highlights opportunities for future investigation and eventual intervention development.

Interpretation of Results Based upon Study Aims

Results contribute new knowledge regarding associations between the outcome variable of interest and the independent variables included in this study. We expected that increased ICU length of stay, longer duration of mechanical ventilation, single ventricle physiology, and higher number of previous surgeries would each be associated with increased PTSS (Aim One, see Chapter Two). None of these variables were significantly associated with the child's reported number of post-traumatic stress symptoms. This suggests that patient-specific biological or clinical variables not explored in the current study may impact the development of PTSS postoperatively. For example, age was associated with PTSS; children who were older at the time of their most recent surgical intervention had significantly higher PTSS burden according to YCPC scores. While age was not one of our hypothesized independent variables, we explored this relationship because of the significant age differences between children with single- and bi-ventricular physiology.

We also hypothesized that opioid administration would be associated with lower PTSS in preschool children after cardiac surgery (Aim Two, Chapter Three). Interestingly, the total amount of opioid received did not correlate with post-traumatic stress symptoms. When we examined each opioid drug independently, only morphine demonstrated a significant, favorable effect on PTSS. Further investigation is warranted to determine if morphine demonstrates a favorable impact on PTSS; this may reflect confounding factors such as the healthcare team's perception of the preschool child's pain when selecting morphine versus other pharmacologic agents.

Finally, we anticipated that parental stress would be associated with PTSS in their preschool children who survived cardiac surgery (Aim Three, Chapter Four). Our data did not reflect a significant relationship between parenting stress related to having an ill child and child PTSS. The implications of this finding are unclear.

Comparison to Existing Research

Our study offers an interesting comparison to the existing research. While previous researchers have explored post-traumatic stress in both preschool-aged children and in CHD, no known studies exist which specifically evaluate PTSS in preschool-aged children after cardiac surgery. Therefore, our study represents a novel contribution to the science. Our study was similar in design to existing literature, in that much of the literature regarding PTSS in young children reflects cross-sectional, descriptive studies. Parent-report tools, such as the YCPC used here, or clinical assessments by trained interviewers, have been frequently used.

The results of our study were consistent with existing research in that treatment variables describing the child's surgical course, evaluated as Aim One of this study, were not significantly correlated with PTSS. Our results from Aim Two of this study, evaluating the relationship between PTSS and post-operative opioid administration, were inconclusive. Previous studies have shown varying benefit between opioid administration and post-traumatic stress in preschool-aged children, with morphine demonstrating greater benefit than other opioid drugs. Similarly, when evaluating the total sample, we saw no statistically significant associations between total opioid dosing and post-traumatic stress. However, when comparing children with single-ventricle versus two-ventricle cardiac physiology, we discovered that morphine, but not other opioids, *did* show a favorable relationship between administered morphine dose and decreased PTSS. Ours is the first known study to evaluate this finding in children following cardiac surgery.

Our study differed from previous research regarding parental stress in two important ways. First, we chose to investigate the relationship between parental stress as an independent variable and child PTSS, rather than parental post-traumatic stress. Second, our study allowed both mothers and fathers to participate as the "primary caregiver." Much of the existing research focuses exclusively on mothers or maternal figures. Our work is an important step towards improving the representation of fathers and paternal caregivers in pediatric research.

Limitations

Results of this study must be interpreted with consideration to its methodologic and conceptual limitations. First, this is a retrospective study involving medical chart review, which introduced challenges for the operationalization of pain in this age group. Given the well-described inconsistencies in rating and documenting pediatric pain, particularly when children are sedated postoperatively (Laures et al., 2019), we used quantity of opioids administered as a key variable of interest in Aim Two of the study. In the future, researchers should consider determination of an *a priori* method of pain assessment to be documented consistently throughout the hospital stay. Additionally, the small sample size of this project limits generalizability to the national and international CHD community. Future multi-site studies would allow for increasingly powerful sample sizes and for more robust statistical analysis.

The role of cognitive impairment in post-traumatic stress responses is not well-defined within this proposed work. The majority of research with PTSD or PTSS excludes children and adults with cognitive impairment, although there is no consensus for a threshold of impairment which precludes inclusion of these individuals. However, the assessment of PTSS in preschool children using the YCPC relies on parent reporting based on parental interpretations of the child's behavior at baseline compared to his or her behavior following a potentially traumatic event. In this sense, the ambiguity surrounding cognitive impairment in the context of PTSS assessment is an acceptable limitation for this study, as there is no need for the child to express his or her own symptom burden. Another conceptual limitation of this study is the exclusion of other complex phenomena which may be related to PTSS in early childhood, such as parent-child attachment and delirium. Both overlap conceptually with early-childhood post-traumatic stress but were excluded here due to feasibility.

Finally, the potential for selection bias exists, as caregiver's willingness to participate may have been influenced by their perception of the child's mental health at the time of enrollment. For example, one family who declined participation stated, "He's doing okay and we don't want to do anything like that." Despite these limitations, however, this study represented a novel contribution to the science by giving attention to the development of PTSS in preschool-aged children after cardiac surgery.

Implications for Practice

The results of our study reveal important implications for the care of children requiring cardiac surgery. First, 11.6% of the participants in our study described levels of PTSS in their children sufficient to achieve the "probable diagnostic threshold" for PTSD according to the YCPC. This is in contrast to the expected incidence of 4-6% of preschoolers with PTSD (Children's Hospital of Philadelphia, 2021). Clinicians who provide follow-up care for young children following cardiac surgery must be open to the potential development of PTSS or PTSD. Nurses and other healthcare providers should consider screening for PTSS and be able to initiate referrals to mental health specialists as appropriate. Parents and caregivers of these patients should be provided anticipatory guidance and education about the potential development of PTSS postoperatively.

Implications for Research

Secondary analysis of the existing data is needed to evaluate patterns of responses to individual YCPC items. This would provide additional insight into the specific post-traumatic stress symptoms that preschool children experience following cardiac surgery. Additional work should compare responses between primary and secondary caregivers and between maternal and paternal caregivers. Previous research has shown discrepant patterns of anxiety and depression between mothers and fathers of young children with CHD, although there are no known studies comparing parenting stress as operationalized in our work between mothers and fathers. (McGrath & Kovacs, 2019)

While many of our results were not statistically significant, we did note interesting differences between children with single- versus bi-ventricular physiology. Further studies with larger sample sizes are warranted to explore the nuanced differences between patients with single- and bi-ventricular physiology. Future longitudinal work could explore the long-term trajectory of PTSS postoperatively and its association with other neurocognitive outcomes in this population. Additional work with physiologic measures is necessary to optimize evaluation of PTSS in preschool-aged children and examine response to potential interventions (Yang, Mady, & Linnaranta, 2021).

Finally, we noted that most families included in our study had more than one child. Multiple caregivers endorsed the toll of CHD and cardiac surgery on the patient's siblings, although we did not collect qualitative interview data in accordance with the aims of our study. Future research should examine the impact of childhood CHD and cardiac surgery on siblings of patients, thus taking a family-centered approach to the holistic well-being of these children and their families.

In conclusion, we learned that preschool children may exhibit PTSS following cardiac surgery. Children with single ventricle physiology appear to have different risk factors than children with biventricular physiology. Additional research is warranted to explore biospsychosocial variables which most strongly contribute to – or protect against – the development of PTSS in this vulnerable population.

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