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Effect of Prostaglandin Duration on Outcomes in Transposition of the Great Arteries with Intact Ventricular Septum

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Abstract

Objective—To study the effects of duration of preoperative prostaglandin E1 (PGE) exposure on perioperative outcomes of the arterial switch operation in patients with transposition of the great arteries with an intact ventricular septum (TGA-IVS).

Design—Retrospective chart review

Setting—Pediatric cardiac intensive care unit in a tertiary care children's hospital.

Patients—All patients with TGA-IVS from 1995 to 2008

Outcome Measures—Inotropic score was calculated for all patients in the first 5 postoperative days and maximum inotropic score was recorded. Length of postoperative mechanical ventilation, fluid balance, mechanical ventilation time, as well as ICU and hospital stay were recorded for all patients.

Results—Study population included 59 patients, 41(69%) underwent balloon atrial septostomy. PGE was used in 52 patients, median exposure of 59 hours, range 0 to 272 hours. Longer preoperative PGE exposure was associated with longer preoperative mechanical ventilation ($p < .001$). There was no association between preoperative PGE duration and cardiopulmonary bypass time, cross-clamp time, or total hospital stay. Patients with longer preoperative PGE exposure had a lower postoperative inotrope score (10 v. 15 $p = .02$).

Conclusion—Greater preoperative PGE exposure was associated with prolonged preoperative mechanical ventilation. Longer PGE exposure was associated with lower postoperative inotrope

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requirements. Aggressive efforts to avoid or shorten PGE infusion duration may not be warranted in this population.

Keywords

prostaglandin; transposition of the great arteries; arterial switch operation

Introduction

Transposition of the Great Arteries (TGA) is the most common cyanotic heart defect to present in the immediate newborn period. Prostaglandin E1 (PGE) is frequently used to maintain arterial duct patency and therefore increase systemic oxygen saturation. Concerns exist regarding side effects of PGE preoperatively as well as its potential deleterious effects on intraoperative and postoperative outcomes. These concerns have led to liberal use of the balloon atrial septostomy as well as other medical strategies to maintain oxygen delivery while minimizing exposure to PGE.(1, 2)

While the preoperative goal is to maintain systemic oxygenation, the postoperative period challenge is to maintain adequate systemic cardiac output. The left ventricle often needs significant inotropic support in the postoperative period.(3) Theoretically a patent arterial duct (PDA) in the preoperative period will maintain elevated pulmonary artery and left ventricular pressures, thereby preparing the left ventricle for its sudden exposure to the higher systemic vascular resistance following the arterial switch procedure. Studies on PGE's effect on operative outcomes as well as comparative studies assessing the risk and benefits of managing patients preoperatively with PGE alone versus balloon atrial septostomy to minimize PGE exposure have not been performed. Therefore, controversy remains on the best preoperative management strategy in patients with TGA-IVS.(4–6) The aim of the present study was to explore associations between cumulative duration of PGE exposure and intraoperative and postoperative outcomes.

Material and Methods

Study Patients

Patients were included if they had a diagnosis of TGA-IVS and underwent an arterial switch operation (ASO) at our institution; a tertiary referral center, between the years of 1995 to 2008. In order to decrease intraoperative variability, we only included patients having surgery by a single surgeon who operated during the entire enrollment period (excluding only 2 patients). Exclusion criteria included incomplete medical records (1 patient) which prevented determination of prostaglandin exposure, intraoperative death (1 patient) which prevented collection of postoperative data, and postoperative use of extracorporeal membrane oxygenation (1 patient) which was felt to independently effect fluid balance, inotrope score, ventilation time, and ICU and hospital length of stay. Hospital records including daily progress notes, operative and discharge summaries, nursing flow sheets, pharmacy records and ventilator records were reviewed for each patient. All patients were preoperatively managed by the Pediatric Cardiology team either in a designated Pediatric Cardiac Intensive Care Unit or Neonatal Intensive Care Unit. All patients were managed postoperatively in the designated Pediatric Cardiac Intensive Care Unit and then the inpatient pediatric cardiology floor. The Medical University of South Carolina Institutional Review Board approved the study protocol.

PGE and preoperative variables

Duration of PGE exposure was determined by reviewing preoperative nursing flow sheets and rounded to the nearest hour of cumulative exposure. The dosage of PGE across the

study period was very uniform with all patients receiving a dose of 0.03–0.05 micrograms per kilogram per minute with bias towards receiving the lower dose. Therefore, we considered only the duration of PGE when analyzing our data. Other preoperative variables recorded included gestational age at birth, birth weight, gender, performance or not of a balloon atrial septostomy, maximum preoperative inotrope score, and preoperative mechanical ventilation hours. Coronary anatomy was described and considered abnormal if there was an arrangement other than a left main coronary artery originating from sinus 1 (left-facing sinus) that gave rise to the left anterior descending and circumflex artery and a right coronary artery that originated from sinus 2 (the right facing sinus).

The preoperative management of each patient was at the discretion of the attending cardiologist and was not determined by a set protocol. During this time period, there was an institutional bias towards performing a balloon atrial septostomy in all patients with TGA-IVS who had either systemic desaturation, reverse differential cyanosis, or in those with a small atrial communication, generally defined as a defect smaller than 5 millimeters by echocardiogram.

Intraoperative and Postoperative Variables

Intraoperative variables included total cardiopulmonary bypass time, cross clamp time, and age at surgery. Postoperative maximum inotrope score was calculated based on that by Kulik *et al.*, and was used to represent the maximum dosages of inotropic agents administered to the patient during their ICU stay.⁽⁷⁾ It is calculated as follows: [Dopamine + Dobutamine in mcg/kg/min] + [Epinephrine in mcg/kg/min $\times$ 100] + [Milrinone in mcg/kg/min $\times$ 10] + [Vasopressin in units/kg/min $\times$ 10,000]. Net fluid balance was measured as the sum of intravenous fluids, blood products or enteral nutrition minus the sum of urine output, mediastinal, pleural or peritoneal drainage over the first 120 postoperative hours. Postoperative ventilator hours and duration of intensive care unit and hospital stay were also collected.

Statistical Methods

Associations were explored between perioperative variables and PGE duration analyzed in a dichotomous fashion. Patients were dichotomized based upon quartiles, the upper quartile of prostaglandin duration (cumulative prostaglandin hours 89 hours and greater) were compared to all others (less than 89 hours of exposure). Prolonged hospital, ventilator and ICU duration data from a single outlier with a congenital airway abnormality not related to his cardiac disease was excluded from the analyses. Groups were compared using, Wilcoxon Rank Sum Test, and Fisher's Exact Test. Statistical significance was defined as *p* less than 0.05.

Results

The median age at arterial switch was 6 days, range 3 to 31 days. Birth weight was median of 3.3 kilograms, and a range of 2.2 kilograms to 4.3 kilograms, 5 patients weighed less than 2.5kg. The median cumulative exposure to PGE was 59 hours; however, it varied widely from no exposure to 272 hours. Preoperative PGE exposure of any length occurred in 88% (52 out of 59). A large portion of our patients underwent a balloon atrial septostomy (41 out of 59, 69%), likely related to our institutional bias to reduce preoperative PGE exposure. The median postoperative hospital stay was 10 days with 6 of those days in the intensive care unit. Median postoperative ventilator hours were 69 and the median maximum inotrope score was 13. These findings are summarized in table 1.

Table 2 summarizes the associations between PGE exposure and preoperative variables. Specifically, cumulative PGE exposure was not related to gender, coronary anatomy, or preoperative inotrope score. Patients with birth weight less than or equal to 2.5 kilograms had similar exposure to prostaglandin as those above 2.5 kilogram. Patients who underwent a balloon atrial septostomy did not differ in their total duration to PGE from those who did not have a balloon atrial septostomy (51 vs. 61 hours, $p=0.18$).

Table 3 displays preoperative and intraoperative variables for patients in the upper quartile of PGE exposure (greater than 89 hours) versus all other subjects. The upper quartile group did not differ from all others in all preoperative and intraoperative variables except for a longer median time of preoperative mechanical ventilation (119 hours versus 59 hours, $p<0.001$).

Table 4 compares postoperative outcomes in the upper quartile PGE exposure group with all other subjects. The two groups did not differ in ventilator time, net fluid balance, postoperative intensive care unit stay or hospital stay. However, the longer duration PGE quartile group did have a significantly lower median maximum inotrope score in the postoperative period (10 versus 14, $p=0.03$).

Discussion

These results indicate that longer PGE exposure has little to no negative effects on operative outcomes. Longer PGE exposure preoperatively was associated with longer preoperative mechanical ventilation. However, the patients with prolonged PGE exposure did have lower postoperative inotrope requirements. Indicating that a patent ductus arteriosus and higher pulmonary artery pressures may help better prepare the left ventricle postoperatively. Longer preoperative PGE exposure was not associated with a longer postoperative ICU or hospital stay.

Routine use of pulse oximetry in the intensive care unit has led to more frequent use of PGE preoperatively.(8) However, the effects of PGE on operative outcomes have only recently been described in a small study.(8) At most pediatric centers, a generally accepted management strategy has been to reduce exposure of PGE inpatients with TGA. A balloon atrial septostomy is often performed as a routine preoperative palliation to improve mixing and reduce PGE exposure. In the current study 69 percent of patients had a balloon atrial septostomy. However, those patients who had a balloon atrial septostomy did not have a significantly decreased exposure to PGE compared to those without atrial septostomy. The optimal timing of discontinuation of PGE infusion after a successful balloon septostomy remains unclear. Early reports of the use of PGE in this population suggest that it should be used for as short a period as possible in order to facilitate the normal reduction in pulmonary vascular resistance.(9) However, recently early discontinuation of PGE after balloon atrial septostomy has been associated with rebound hypoxemia.(10) An association between PGE use after atrial septostomy and increased postoperative stay has been reported, however, this was a comparison of only 26 patients.(8) Our current study has a larger sample size and showed no association between hospital stay and longer preoperative PGE exposure.

Maximum inotrope score has been recently described as a predictor of morbidity and mortality in infants after congenital heart surgery requiring cardiopulmonary bypass.(11) It is widely accepted that the left ventricle quickly loses the ability to generate systemic pressure over time without an additional ventricular or great artery shunt in TGA. This has led to the common practice of performing the ASO within the first two weeks of life in those who present in the immediate newborn period. Pulmonary artery banding, as well as pulmonary artery banding with ductal stenting has been described as methods to prepare the

left ventricle in “late presenters”.(12–15) We found an association between longer duration of preoperative PGE and a lower postoperative maximum inotrope score. The importance of a PDA in patients to assist with left ventricle preparedness within the first two weeks of life is not known. Although the median age at reparative surgery in our cohort was 6 days, our data suggests a potential benefit between retaining ductal patency with PGE and a better prepared left ventricle within the first two weeks of age.

Due to the retrospective nature of our study and large time span, our study has multiple limitations. Unfortunately, other secondary signs of postoperative cardiac output such as mixed venous saturation and lactic acid level were not recorded or too infrequently recorded in order to be included. More frequent preoperative echocardiograms to measure PDA size as well as left ventricular mass, volume and function would also be helpful in establishing causality between ductal patency and better left ventricle preparedness for the postoperative systemic circulation. The large time span of our study leads to confounding influences such as changes in perioperative management strategies.

Conclusion

Prolonged PGE exposure was associated with a prolonged preoperative mechanical ventilation, but also associated with lower postoperative inotrope requirements. Performing a balloon atrial septostomy did not reduce preoperative exposure to PGE. Most importantly, there were no deleterious effects of prolonged preoperative PGE use on intraoperative and postoperative outcomes. Therefore, the data suggests that uniform methods to aggressively wean off of PGE may not be warranted given the risk: benefit ratio suggested in this study. A large prospective study of neonates with TGA-IVS with close monitoring of preoperative echocardiographic measures, such as left ventricular mass and volume, as well as close monitoring of postoperative measures of cardiac output is necessary to better delineate PGE’s effect on postoperative outcomes. Such a study would likely need multi-institutional involvement.

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Table 1

Demographics Characteristics of 59 Patients with TGA/IVS

Category	Median	Interquartile range
Birthweight (kilograms)	3.3	2.9–3.55
Age at Surgery (days)	6	5–8
Preoperative Prostaglandin (hours)	59	18–90
Cardiopulmonary Bypass Time (minutes)	170	157–180
Cross Clamp Time (minutes)	82	75–85
Postoperative Ventilator Time (hours)	69	46–111
Postoperative Maximum Inotrope Score	13	10–15
Postoperative Intensive Care Unit (days)	6	5–7
Postoperative Hospital Stay (days)	10	8–13

TGA/IVS: Transposition of the great arteries with intact ventricular septum

Table 2

Associations between PGE and preoperative variables

Category	N	Median Prostaglandin Exposure (hours)	p-value
female	19	41	0.47
male	40	60	
abnormal coronary anatomy	18	67	0.53
normal coronary anatomy	71	54	
balloon atrial septostomy	41	51	0.18
no balloon atrial setpstomy	18	61	
intubated at time of surgery	8	84	0.03
extubated at time of surgery	51	52	
birthweight ≥ 2.5 kilograms	54	57	0.52
birthweight < 2.5 kilograms	5	58	

Table 3

Preoperative and Intraoperative Variables by PGE group

Category	Upper Quartile	1–3 rd Quartiles	p-value
Birth weight (kilograms)	3.3	3.1	0.72
Presence of Coronary Anomaly	28%	31%	1
Male	80%	65%	0.1
Balloon Atrial Septostomy	60%	69%	0.59
Preoperative Ventilator Time (hours)	119	59	<0.01
Intubated at Time of Surgery	20%	9%	0.08
Preoperative Maximum Inotrope Score	5	2	0.44
Age at Surgery (days)	7	6	0.15
Cross Clamp Time (minutes)	78	80	0.22
Cardiopulmonary Bypass (minutes)	174	175	0.52

* displayed values for numerical variables are medians, percentages are displayed for categorical data*

Table 4

Postoperative Variable Compared by Quartiles of PGE Duration

Category	Upper quartile median	1–3rd quartiles median	p-value
Ventilator Time (hours)	98	95	0.87
Maximum Inotrope Score	10	15	0.02
Net Fluid Balance (cc)	−509	−466	0.41
ICU stay (days)	6.5	6	0.81
Hospital Stay (days)	10	10	0.75