Treprostinil Improves Persistent Pulmonary Hypertension Associated with Congenital Diaphragmatic Hernia

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Objective To evaluate the effect of continuous treprostinil in infants with severe pulmonary hypertension associated with congenital diaphragmatic hernia (CDH) on specific markers of pulmonary hypertension severity and to report the safety and tolerability of treprostinil.

Study design We conducted a retrospective cohort study of infants with CDH-associated pulmonary hypertension treated with treprostinil from January 2011 to September 2016. Severity of pulmonary hypertension was assessed by echocardiogram and serum B-type natriuretic peptide (BNP) by using time points before initiation and 24 hours, 1 week, and 1 month after treprostinil initiation. Fisher exact tests, Wilcoxon-rank sum tests, and mixed-effects models were used for analysis.

Results Seventeen patients were treated with treprostinil for a median of 54.5 days (IQR 44.3-110 days). Compared with the concurrent CDH population (n = 147), infants treated with treprostinil were more likely to require extracorporeal support (76.5% vs 25.2%, $P < .0001$), to have a longer hospital stay (144 vs 60 days, $P < .0001$), and to need longer mechanical ventilator support (76.5 vs 30.9 days, $P < .0001$). Following treprostinil initiation, there was a significant reduction in BNP at 1 week (1439 vs 393 pg/mL, $P < .01$) and 1 month (1439 vs 242 pg/mL, $P = .01$). Severity of pulmonary hypertension by echocardiogram improved at 1 month (OR 0.14, CI 95% 0.04-0.48, $P = .002$). Despite these improvements, overall mortality remained high (35%). There were no adverse events related to treprostinil, including no hypotension, hypoxia, or thrombocytopenia.

Conclusions In this cohort, treprostinil use was associated with improved severity of pulmonary hypertension assessed by echocardiogram and decreased BNP, with no significant side effects. *(J Pediatr 2018;■■:■■-■■).*

Congenital diaphragmatic hernia (CDH) is a major congenital anomaly affecting ~1:3000-1:4000 live births.[1-5] Despite advancements in surgical techniques and pharmacologic and respiratory-support strategies, mortality remains 20%-30% at tertiary care centers.[6,7] Pulmonary hypertension, an abnormal elevation of pulmonary artery pressure, is associated with significant morbidity and mortality in infants with CDH.[8] Although pulmonary hypertension is present in most infants in the immediate neonatal period, persistent severe pulmonary hypertension beyond the first few weeks of life is associated with increased morbidity, including ventilator days and extracorporeal membrane oxygenation (ECMO), and mortality.[8-10] In a cohort of infants with CDH from 1991 to 2002, Dillon et al found no survivors among infants with severe, persistent pulmonary hypertension at 6 weeks of age, despite medical therapies including inhaled nitric oxide and ECMO.[10]

Treprostinil is a synthetic prostacyclin analog and potent pulmonary vasodilator that is approved for the treatment of idiopathic pulmonary arterial hypertension in adults.[11,12] In addition to inhaled nitric oxide and sildenafil, treprostinil has been used to treat severe, refractory pulmonary hypertension associated with CDH in infants.[13-15] Evidence to support its use remains limited to a retrospective review of treprostinil among a heterogeneous population of infants with pulmonary hypertension that found treprostinil to be well tolerated, although the authors did not investigate its ability to modulate pulmonary hypertension severity,[13] and several case series of infants with CDH showing clinical improvement after treprostinil initiation.[14,15] In this study, we sought to evaluate treprostinil treatment of pulmonary hypertension associated with CDH using specific markers of pulmonary hypertension severity, echocardiogram and serum B-type natriuretic peptide (BNP), as well as to evaluate the safety and tolerability of treprostinil in this population.

BNP	B-type natriuretic peptide
CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation
LHR	Lung area to head circumference ratio
RVSP	Right ventricular systolic pressure

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Methods

We performed a retrospective chart review of patients diagnosed with CDH treated at the Children's Hospital of Philadelphia and enrolled in the Pulmonary Hypoplasia Program study, a single-center prospective registry. We included patients treated from January 2011 until September 2016, as this corresponded with available electronic medical records. All patients with CDH were eligible for enrollment in the Pulmonary Hypoplasia Research Program study (n = 167), and all patients who provided consent (n = 164) were included in this analysis. The study was approved by the Children's Hospital of Philadelphia institutional review board, Committee for the Protection of Human Subjects (institutional review board no. 06-003779).

Patients with a diagnosis of CDH who received treprostinil during their initial hospitalization were identified through the electronic pharmacy order entry system. Recorded data on patient demographics, prenatal course and imaging, and postnatal care, including surgical repair, vital signs, laboratory values, and medication use, were analyzed. When available, prenatal imaging including detailed ultrasonography scan and ultrafast fetal magnetic resonance imaging was used to calculate observed/expected lung area to head circumference ratio (LHR) and fetal lung volumes as previously described.[16,17] Echocardiograms were obtained as part of routine clinical practice, typically at hospital admission and as clinically indicated. BNP values typically were obtained weekly or more frequently during treatment changes at the discretion of the treating providers. Categorical variables were analyzed with χ^2 or Fisher exact tests and continuous variables by Wilcoxon rank-sum tests. A linear mixed-effects model was used to analyze BNP change over time. In addition, to determine whether age at initiation altered results observed over time, the model was adjusted for chronologic age at initiation.

Treprostinil was begun at the discretion of clinical providers for patients with a diagnosis of CDH and evidence of significant pulmonary hypertension by clinical assessment, including BNP elevation and echocardiogram, despite inhaled nitric oxide administration. Patients with uncontrolled coagulopathy, history of grade 3 or 4 intracranial hemorrhage, or refractory hypotension were typically excluded from consideration for treatment. In patients who were treated with treprostinil, the medication generally was initiated at a dose of ~4 ng/kg/min given intravenously through a central venous line and titrated up over a period of days to clinical effect, typically to a dose of 20-30 ng/kg/min. Doses were adjusted for weight gain at the discretion of the treating provider, typically with weight gain of >10% of body weight.

For patients treated with treprostinil, we reviewed images from clinically indicated echocardiograms performed via standard pediatric views on a Phillips IE33 machine (Phillips, Andover, Massachusetts). Images were digitally stored using Syngo Dynamics (Siemens, Ann Arbor, Michigan). Transthoracic echocardiograms performed before the initiation of treprostinil and at approximately 1 week, 1 month, and 6 weeks after initiation were reviewed offline in a standardized manner by a reader blinded to treatment and outcome. Echocardiographic assessment of pulmonary hypertension included right ventricular systolic pressure (RVSP) using peak tricuspid regurgitation Doppler jet velocity, direction of flow across a patent ductus arteriosus if present, and interventricular septal position, in a manner similar to previously described methods.[4,5,14] RVSP measurements were compared with the systolic blood pressure at the time of echocardiogram. Severity of pulmonary hypertension was graded as mild/none (RVSP less than one-half systemic), moderate (RVSP one-half to systemic), or severe (RVSP greater than systemic). RVSP was estimated by the use of tricuspid regurgitation jet velocity measured by continuous-wave Doppler using the modified Bernoulli equation ($4V^2$) without correction for right atrial pressure. When present, the direction of blood flow across the patent ductus arteriosus was assessed with left-to-right flow scored as mild, bidirectional shunting scored as moderate, and pure right-to-left shunting scored as severe pulmonary hypertension. Finally, qualitative assessment of interventricular septal flattening at end systole was graded as rounded (none/mild), flat (moderate), or bowing into the left ventricle (severe).

To analyze echocardiographic outcomes over time, binary generalized estimating equation models were used to model the odds of severe pulmonary hypertension after treatment. To determine whether age at initiation altered results observed over time, models were adjusted for chronologic age at initiation. In patients for whom long-term analysis was not possible due to early death, data points were coded as missing in the statistical models. Statistical significance was accepted at $P < .05$. All data analysis was conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

This retrospective cohort included a total of 164 infants with CDH, 17 of whom were treated with treprostinil for severe pulmonary hypertension. Patient demographics, prenatal imaging, and outcomes for the cohort are summarized in the **Table**. The cohort treated with treprostinil and general cohort with CDH were not significantly different for infant sex, mean gestational age at delivery, or mean birth weight. There were also no significant differences in frequency of right-sided CDH, intrathoracic liver position, or presence of other congenital anomalies. However, there was significantly greater lung hypoplasia by prenatal assessment in the treprostinil group with a lower mean ultrasound LHR and mean observed/expected LHR. Infants treated with treprostinil had greater maximum BNP during their hospitalization that peaked later, consistent with severe, late pulmonary hypertension. Infants treated with treprostinil were more likely to be treated with additional pulmonary hypertension therapies, including inhaled nitric oxide, sildenafil, prostaglandin E1, and ECMO. They were also more likely to have a longer length of hospital stay and longer duration of mechanical ventilation. Although overall mortality was not different between the groups, the cohort

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