JPPT | Retrospective Case Series

Transitioning From Intravenous to Subcutaneous Prostacyclin Therapy in Neonates With Severe Pulmonary Hypertension

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This article aims to present our neonatal intensive care unit experience transitioning from intravenous epoprostenol to IV and subcutaneous treprostinil in patients with persistent pulmonary hypertension of the neonate. This was a retrospective chart review at an academic teaching hospital. Neonates with a diagnosis of persistent pulmonary hypertension of the neonate (PPHN) who were started on IV prostacyclin therapy while admitted to the NICU between August 2017 and October 2019 were included. Of the 5 patients included, gestational ages ranged from 24 to 38 weeks. All patients were treated with inhaled nitric oxide and sildenafil before being initiated on IV or SQ prostacyclin therapy. Intravenous epoprostenol dosing was initiated at 1 ng/kg/min and was increased by 1 ng/kg/min every 12 hours until the provider was satisfied with the clinical response. Once the dose was stable for a few days epoprostenol was transitioned to IV treprostinil using double the last epoprostenol dose. A few days later infants were switched to SQ treprostinil using the same dose by stopping the IV infusion and starting the SQ infusion. All patients survived to hospital discharge and were sent home on SQ treprostinil. Minimal adverse effects were seen; patients experienced some slight hypotension, tachycardia, and diarrhea. Severe pulmonary hypertension is a common occurrence and a significant cause of mortality in the NICU. Our patients demonstrate that IV and SQ prostacyclin therapy is a therapeutic option for PPHN. Additionally, rapid high-dose transition from IV epoprostenol to IV treprostinil and then to SQ treprostinil is well tolerated in neonates, with minimal adverse effects.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia; cGMP, cyclic guanosine monophosphate; ECMO, extracorporeal membrane oxygenation; FDA, US Food and Drug Administration; GA, gestational age; iNO, inhaled nitric oxide; IV, intravenous; NICU, neonatal intensive care unit; PDE 5, phosphodiesterase 5; PPHN, persistent pulmonary hypertension of the neonate; SQ, subcutaneous

KEYWORDS congenital diaphragmatic hernia; epoprostenol; neonatal intensive care unit; prostacyclin; pulmonary hypertension; treprostinil

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Introduction

Persistent pulmonary hypertension of the neonate (PPHN) affects more than 10% of infants admitted to the intensive care unit with respiratory failure, which is responsible for more than one-third of all neonatal mortality.[1] Neonates who have a difficult time transitioning to extrauterine life may develop PPHN due to the persistence of fetal circulation. Infants born prematurely or with congenital defects, such as severe diaphragmatic hernias, often have impaired pulmonary function due to the disruption of pulmonary vascular growth, which can also result in pulmonary hypertension. Current therapy for congenital diaphragmatic hernia (CDH)–associated PPHN consists of supportive care, including ventilation, corrective surgery, and extracorporeal membrane oxygenation (ECMO) if necessary.[2] Common pharmacotherapy agents used to treat PPHN include inhaled nitric oxide (iNO) and phosphodiesterase inhibitors.[3]

Prostaglandin therapy is commonly used for pulmonary arterial hypertension in adult patients, but there is a paucity of data regarding the use in neonates, specifically dosing, transitioning between agents, and administration routes. Our objective is to present a case series describing the use of IV prostacyclin, including converting between epoprostenol and treprostinil, as well as transition to SQ treprostinil in neonates with PPHN.

Methods

This case series includes patients admitted to a single NICU during a 26-month period (August 2017 through October 2019) who were given a diagnosis of PPHN and were started on IV prostacyclin therapy. A total of 5 patients were included in this case series. Data

included were descriptive in nature and focused on the dosing and transition of IV epoprostenol and treprostinil therapy to SQ treprostinil therapy. The manuscript was approved for submission after review by the facility compliance professional.

Results

Reported data were extracted from patient's individual medical records and included age, diagnoses, and medical treatment plans. All patients received iNO and sildenafil prior to the initiation of prostacyclin therapy. The maximum iNO dose administered was 20 parts per million. Sildenafil doses ranged depending on the response to therapy, but they remained between the typical dose of 0.5 to 3 mg/kg every 8 hours for term infants. Prostacyclin analogues were initiated when pulmonary hypertension symptoms did not improve on iNO and sildenafil therapy alone. Intravenous prostacyclins were administered using Alaris Medley Syringe pumps with concentrations ranging from 1000 to 5000 ng/mL. Subcutaneous infusions were administered using CADD MS3 pumps and Cleo 90 infusion sets (tubing plus 6-mm cannula, supplied by Smiths Medical, Inc., Minneapolis, MN) with concentrations ranging from 0.1 to 1 mg/mL. Subcutaneous concentration dilutions with normal saline were necessary to allow for suitable dose titration volumes. Table 1 summarizes the clinical details of the patients transitioned from IV epoprostenol to SQ treprostinil.

Patient 1. A female neonate who was born at 37 weeks gestational age (GA) was admitted to the NICU with an undiagnosed large left-sided CDH, PPHN, and respiratory failure. She required high-frequency oscillatory ventilation, nitric oxide, and eventually venoarterial ECMO. The CDH was surgically repaired on day of life 7 during ECMO support. Despite the addition of sildenafil she was unable to be weaned from ECMO. After nearly a month of ECMO support, IV epoprostenol was initiated at 1 ng/kg/min on day of life 28 and was titrated up by 1 ng/kg/min every 12 hours until 10 ng/kg/min. Within 72 hours of epoprostenol, the baby was able to be weaned from ECMO. Epoprostenol was transitioned to IV treprostinil by using a high-dose rapid transition on day of life 57 by reducing the epoprostenol to 5 ng/kg/min and starting the IV treprostinil at 10 ng/kg/min. Roughly 24 hours later the epoprostenol was discontinued and treprostinil was increased to 20 ng/kg/min. This transition was slightly less aggressive compared with patients 2 to 5 because it was the first use of prostacyclin analogues in an infant at this institution. The infant tolerated the transition well, with minimum adverse reactions. Intravenous treprostinil was titrated up to a dose of 21 ng/kg/min then transitioned to SQ at 26 ng/kg/min by simultaneously stopping the IV therapy and starting the SQ infusion on day of life 77. The large increase in dose was due to SQ pump administration limitations. The neonate tolerated the transition well, experiencing some slight hypotension (76/29) about 2 hours after the start of the SQ infusion, tachycardia, and diarrhea.

Patient 2. A male neonate who was born at 39 weeks GA with a severe left-sided CDH developed pulmonary hypertension and respiratory distress after delivery, requiring intubation and IV prostacyclin therapy. Epoprostenol was started on day of life 1 at 1 ng/kg/min then titrated up by 1 ng/kg/min every 12 hours to 11 ng/kg/min. The CDH was surgically repaired on day of life 4. Epoprostenol was transitioned to treprostinil on day of life 21 by initiating IV treprostinil at 22 ng/kg/min and stopping epoprostenol. The infant tolerated the transition well with minimum adverse reactions. Once the patient was stable, IV treprostinil at 22 ng/kg/min was transitioned to SQ at 21 ng/kg/min on day of life 24 by simultaneously stopping the IV therapy and starting the SQ infusion. Subcutaneous pump administration limits prevented conversion from IV to SQ at 1:1 ratio. The neonate tolerated the transition well, experiencing tachycardia and diarrhea.

Patient 3. A female neonate who was born at 24 weeks GA developed acute severe hypoxic respiratory failure requiring reintubation and oscillation support around 45 weeks postmenstrual age (about 4.5 months after delivery) due to chronic lung disease of prematurity. On day of life 142, she was started on IV epoprostenol shortly after the decompensation because of severe pulmonary arterial hypertension. Epoprostenol was titrated to 10 ng/kg/min, and then transitioned to IV treprostinil at 18 ng/kg/min by stopping the epoprostenol infusion and then starting the treprostinil infusion. The neonate tolerated the transition very well and was then started on SQ treprostinil on day of life 158 at 19 ng/kg/min. Once stable, the infant was discharged to a local children's hospital for further care.

Patient 4. A female neonate who was born at 38 weeks GA with a known severe right-sided CDH developed pulmonary hypertension and respiratory distress after delivery and ultimately required venoarterial ECMO. Intravenous epoprostenol was initiated at 1 ng/kg/min prior to cannulation and was titrated up by 1 ng/kg/min every 12 hours to 18 ng/kg/min. After requiring two corrective surgeries for the CDH, on days of life 5 and 16, because of bleeding complications, the patient was de-cannulated and transitioned to IV treprostinil at 38 ng/kg/min. Intravenous treprostinil was transitioned to SQ treprostinil at 39 ng/kg/min on day of life 22, with no adverse events.

Patient 5. A male neonate born at 33 weeks GA who received a diagnosis of tricuspid regurgitation, right ventricle dysfunction, and severe PPHN required intubation in the delivery room and escalation of respiratory support. He was started on IV epoprostenol at 1 ng/kg/min and was titrated to 14 ng/kg/min. On day of life 9, the patient was transitioned to IV treprostinil at 28 ng/kg/min, which was then titrated up to 33 ng/

Table 1. Clinical Details of Patients Transitioned From IV to SQ Prostacyclin Therapy

Case No. (Sex)	BW (GA)	Diagnosis	Epoprostenol Dose, ng/kg/min			Treprostinil Dose, ng/kg/min			DOL at Discharge
			Support	Initial IV Dose (Maximum Dose)	DOL Initiated	IV Transition From Epoprostenol (Maximum Dose)	DOL Initiated	Discharge SQ Maximum Dose	
1 (F)	2.78 kg (37 wk)	Undiagnosed large left-sided CDH, respiratory failure, PPHN	Mechanical ventilation, venoarterial ECMO support (month-long course)*	1 (10)	28	Epoprostenol initiated at 10 ng/kg/min, then reduced to 5 ng/kg/min IV treprostinil increased to 20 ng/kg/min, then IV epoprostenol stopped (21)	77	26	125
2 (M)	2.96 kg (39 wk)	Severe left-sided CDH, respiratory failure, PPHN	Mechanical ventilation	1 (11)	1	IV treprostinil initiated at 22 ng/kg/min, then IV epoprostenol stopped (22)	24	21	50
3 (F)	0.61 kg (24 wk)	Extreme prematurity, respiratory failure, Severe PPHN	Reintubation at 4.5 mo of age Mechanical ventilation	1 (10)	142	IV treprostinil initiated at 18 ng/kg/min, then IV epoprostenol stopped (18)	158	19	162
4 (F)	3.01 kg (38 wk)	Severe right-sided CDH, respiratory failure, PPHN	Mechanical ventilation, VA-ECMO	1 (18)	0	IV treprostinil initiated at 38 ng/kg/min, IV epoprostenol stopped (38)	22	39	73
5 (M)	2.06 kg (33 wk)	Tricuspid regurgitation, right ventricle dysfunction, possible coarctation, respiratory failure, and severe PPHN	Mechanical ventilation	1 (14)	3	IV treprostinil initiated at 28 ng/kg/min, then IV epoprostenol stopped (33)	19	38	69

BW, birth weight; CDH, congenital diaphragmatic hernia; DOL, day of life; ECMO, extracorporeal membrane oxygenation; GA, gestational age; PPHN, persistent pulmonary hypertension of the neonate

* Patient was able to be weaned from ECMO support within 72 hours of epoprostenol initiation.

Table 2. ECHO Findings/Oxygen Index Prior to Prostacyclin Therapy, at Transition to SQ Treprostinil, and Closest to Discharge

Case and ECHO	Right Ventricle Characteristics				PDA and Direction of Shunt	Peak Oxygen Index
	Size	Dilation	Hypertrophy	Systolic Pressures		
1						
Pre	Mild enlargement	Yes	Yes	Greater than ½ systemic by TR jet and PDA flow direction	Large with bidirectional but predominantly right-to-left shunting	60.93
Transition	Normal	No	Yes	Less than ½ systemic	Closed	2.29
Discharge	Normal	No	No	½ systemic by septal position in systole	Closed	NA
2						
Pre	Mild enlargement	No	Yes	50 mm Hg plus the RA mean pressure	Large with low-velocity bidirectional shunt (mostly right-to-left shunting)	23.94
Transition	Normal	No	Yes	Greater than ½ systemic by septal position	Closed	3
Discharge	Normal	No	No	Greater than ½ systemic	Closed	NA
3						
Pre	Normal	Yes	Yes	Elevated based on septal wall position and PDA gradient	Small to moderate with restrictive shunting (mostly left to right)	38.46
Transition	Normal	No	No	Elevated based on septal wall position and PDA gradient	Moderate with low-velocity left-to-right shunting	41.18
Discharge	Patient transferred to local children's hospital					
4						
Pre	Normal	Yes	Yes	Estimated 55 mm Hg plus mean atrial pressure	Large with right-to-left shunting	45.97
Transition	Normal	No	Yes	Estimated 36 mm Hg plus mean atrial pressure	Small with mildly restrictive, bidirectional shunting (right to left in systole and left to right in diastole)	13.55
Discharge	Normal	No	No	Estimated less than ½ systemic by septal position (systole)	Closed	NA
5						
Pre	Normal	Yes	Yes	Estimated 65 mm Hg plus mean right atrial pressure	Moderate with mildly restrictive, nearly continuous right-to-left shunting	40.14
Transition	Normal	Yes	Yes	Estimated 48–52 mm Hg plus mean atrial pressure	Closed	4.19
Discharge	Normal	Yes	Yes	Estimated 45–50 mm Hg plus mean atrial pressure	Closed	NA

ECHO, echocardiogram; RV, right ventricle; PDA, patent ductus arteriosus; RA, right atrium

kg/min based on provider discretion. Subcutaneous treprostinil was initiated on day of life 19 at 33 ng/kg/min and was titrated up to 38 ng/kg/min, which was the dose at time of discharge. The patient tolerated the epoprostenol and treprostinil infusions as well as the transition between routes with no adverse events.

Patients included in this case series experiencing the adverse effects mentioned did not require any interventions, such as fluid boluses or dose adjustments. All patients discharged to home were on SQ treprostinil and oral sildenafil. Echocardiogram results before prostacyclin initiation, closest to SQ transition, and closest to discharge have been included in Table 2.

Discussion

All patients included in this case series received a diagnosis of PPHN, which is a common finding in premature infants and neonates born with CDH. Infants born prematurely often develop chronic lung disease of prematurity, also known as bronchopulmonary dysplasia (BPD), due to the disruption in pulmonary vascular growth, ultimately leading to the development of pulmonary hypertension. Current supportive care to prevent the development of BPD includes noninvasive ventilation techniques and gentle mechanical ventilation if needed.[4] Pharmacologic therapies include administering steroids to mothers prior to delivery and surfactant to premature neonates.[5] If BPD develops later in life, additional interventions include diuretic and steroid therapy. With diaphragmatic hernias, abdominal components enter the chest cavity because of an abnormal opening in the diaphragm, limiting lung development. These patients are typically born with small, structurally abnormal lungs, leading to the development of pulmonary hypertension. Supportive therapy for patients with CDH consists of mechanical ventilation, corrective surgery, and ECMO support if necessary, depending on the severity of the defect.

Pharmacologic mechanisms for pulmonary hypertension treatment focus on pulmonary vasodilation. Current agents used include iNO and phosphodiesterase type 5 (PDE 5) inhibitors.[3] Inhaled nitric oxide causes pulmonary vasodilation by increasing concentrations of cyclic guanosine monophosphate (cGMP) in the pulmonary smooth muscle.[6] PDE 5 inhibitors, such as sildenafil, work on the same pathway by inhibiting the PDE 5 enzyme that breaks down cGMP to guanosine monophosphate, prolonging the action of cGMP.[7] Prostacyclin analogues, such as epoprostenol and treprostinil, work on a separate pathway that causes pulmonary vasodilation by increasing cyclic adenosine monophosphate.[8] These medications are commonly used among adults with severe pulmonary hypertension.

Currently, neither epoprostenol nor treprostinil is approved by the FDA in neonates for the treatment of pulmonary hypertension, leaving very few treatment options in the neonatal population. The available literature on the use of prostacyclin analogues in the neonatal population is sparse, and of the information available, administration and dosing are typically not discussed. McIntyre and colleagues[9] published a report of 36 patients, younger than 12 months, who received IV prostacyclin therapy. Dosing aligned with the case reports mentioned above, with a mean treprostinil dose of 36.44 ng/kg/min in those who survived. They did not describe the logistics of transitioning patients between IV epoprostenol and treprostinil, or from IV to SQ treprostinil. The authors concluded that prostacyclin analogues were tolerated by critically ill infants under the age of 12 months. In addition to the pulmonary vasodilation affects from prostacyclin therapy, undesirable effects, including inhibition of platelet aggregation and smooth muscle proliferation, can occur. However, these effects are minimal and likely clinically insignificant. McIntyre and colleagues[9] reviewed major bleeding events in the aforementioned 36 patients. Two patients experienced hemorrhages (pulmonary and intraventricular) within 48 hours of drug initiation, but both patients had a predisposition to bleed prior to administration of IV prostacyclins. In addition to the adverse effects mentioned above, prostacyclin therapy can also cause systemic hypotension. Of the 36 patients included in the McIntyre et al[9] study, there were 7 total events of hypotension, 5 of which required dose reductions. These patients tolerated subsequent dose increases and did not develop hypotension.

Neonatal administration of IV prostacyclins requires specific medication administration pumps and concentrations because of very low infusion rates. When starting a 3-kg patient on IV epoprostenol at 1 ng/kg/min, a concentration of 1000 ng/mL would result in a rate of 0.18 mL/hr. Often, these infusions are dispensed in syringes because syringe pumps are required to administer low infusion rates. From a stability standpoint, both IV epoprostenol and treprostinil can be used up to 48 hours after preparation if stored in the refrigerator.[10,11] This limitation required nurses to change out syringes every 24 to 48 hours depending on the administration rate. Subcutaneous administration requires the use of an ambulatory pump (e.g., CADD MS3 pump), very similar to an SQ insulin infusion for diabetic patients. The typical concentration used for SQ infusion ranges from 0.1 mg/mL (diluted using normal saline) to 1 mg/mL.

In this case series, both prostacyclin agents were initiated and well tolerated by the neonatal patients. Hypotension and tachycardia were seen, but they did not require any dosing adjustments or interventions. The general approach consisted of starting the infusion of IV epoprostenol at 1 ng/kg/min via central line, then titrating by 1 ng/kg/min every 12 hours based on provider discretion. Intravenous epoprostenol was the drug of choice because of its extremely short half-life of about 6 minutes. If the patient were to develop any adverse reactions, the medication could be stopped

Table 3. Example of IV and SQ Prostacyclin Dosing for a 3-kg Neonate

Concentration, ng/mL	Dose, ng/kg/min	Rate, mL/hr
Intravenous epoprostenol		
1000	1	0.18
1000	10	1.8
Intravenous treprostinil		
1000	20	3.6
3000	20	1.2
5000	20	0.72
Subcutaneous treprostinil		
100,000	25.6	0.046*
100,000	26.7	0.048*
500,000	16.7	0.006*
500,000	22.2	0.008*
500,000	27.8	0.01*
1,000,000	11.1	0.002*
1,000,000	22.2	0.004*
1,000,000	33.3	0.006*

* Microinfusion pump (CADD MS3) can only be programmed in increments of 0.002 mL/hr.

and cleared from the body within 20 minutes. Optimal dosing is a nebulous target. Our experience over the years is that epoprostenol doses of 10 to 20 ng/kg/min provide optimal results in the near term. We have seen that overly aggressive dosing can lead worsening oxygenation and the development of pulmonary edema. Once at the target IV epoprostenol dose, the transition to IV treprostinil was completed by stopping the IV epoprostenol infusion, aspirating the line to prevent any accidental boluses, flushing the line, and then starting the IV treprostinil at double the dose. Work in adults has shown that epoprostenol is between 2 and 3 times as potent as treprostinil. Our practice for more than a decade in adults has been to convert IV epoprostenol to IV treprostinil in a direct 1-step transition at twice the dose. We then titrate up every 4 to 6 hours by 1 to 2 ng/kg/min until the patient experiences mild prostanoid side effects. In neonates we have taken a slightly more gradual uptitration once switched to treprostinil, typically increasing by 1 ng/kg/min every 12 to 24 hours based on clinical response (oxygenation and mechanical ventilator support requirements) at provider discretion.[12,13]

Conversion to SQ treprostinil is accomplished by starting the SQ pump at the same dose and stopping the IV infusion. There are more conservative transition protocols, but we have had 13 years of experience transitioning both adults and neonates from IV epoprostenol to IV treprostinil, and ultimately to SQ treprostinil, in this fashion without problems. Using the SQ route allows for the removal of all IV access points. In our case series several patients were unable to be converted from IV to SQ at 1:1 dose because of limitations of the subcutaneous CADD MS3 pump, which can only be programmed in increments of 0.002 mL/hr. To minimize dose excursions due to the microinfusion pump limitations, we transition most SQ treprostinil patients to the 0.5 mg/mL (500,000 ng/mL) solution. Table 3 highlights dosing and drug concentration considerations when using IV and SQ prostacyclin therapy. This limitation is extremely important to recognize because further titration via the pump may yield large dose increases depending on the treprostinil concentration.

Conclusions

In this case series all patients received IV prostacyclin therapy for pulmonary hypertension during their NICU admission. Intravenous epoprostenol was rapidly transitioned to IV treprostinil (at double the last epoprostenol dose) and then to SQ treprostinil. The conversion between agents and routes of administration was well tolerated, with minimal adverse effects noted in these neonatal patients. Larger studies further evaluating the safety and efficacy of these medications in this population are warranted.

ARTICLE INFORMATION

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Disclosure Dr. Jeremy Feldman is currently a speaker for Gilead Sciences, Inc. and United Therapeutics and a consultant for United Therapeutics, Actelion Pharmaceuticals Ltd., and Acceleron Pharma, Inc. All other authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review and informed consent was not obtained.

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