Effects and Tolerability of Treprostinil in Neonates with Persistent Pulmonary Hypertension

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Abstract

Objective The aim was to establish the effects of treprostinil in congenital diaphragmatic hernia (CDH) patients with persistent pulmonary hypertension (PHT) after one week of treatment. Drug effects were assessed by oxygenation index (OI), clinical end points, serial biochemical markers, and pre- and posttreatment echocardiogram. Treatment complications were also described.

Study Design This is a quasi-experimental study of neonates with PHT admitted to the NICU within 48 hours showing persistent clinical instability, receiving mechanical ventilation with FiO2 $>$ 60%, milrinone therapy, and inhaled nitric oxide. Clinical data were compared before and after treprostinil treatment.

Results Seventeen neonates met the inclusion criteria. Median age was 17 days. Before treatment, median OI was 20 (IQR: 12–27). Suprasystemic PHT was estimated by echocardiogram in 8/17 patients; the rest were systemic. After one week of treatment, 15/17 patients were alive and median OI was 8 (IQR: 5–12, $p = 0.0089$). There were no statistically significant changes in laboratory data. Echocardiogram still showed suprasystemic PHT in 20% of patients. Adverse effects included hypotension, hematoma at the infusion site, and surgical persistent ductus arteriosus (PDA) closure in 4/17 patients. Fourteen patients were discharged. The median treatment time was 61 days.

Conclusion Treprostinil was well tolerated with satisfactory clinical response. Further studies are required to identify early responder subgroups.

Keywords
- newborns
- pulmonary hypertension
- treprostinil
- congenital diaphragmatic hernia
- prostacyclin

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by pulmonary vascular disease presenting as supraphysiological elevation of the pressure in the right side of the heart that induces right-to-left extra pulmonary shunts through persistent ductus arteriosus (PDA) and foramen oval, thereby generating lability and hypoxemia as well as ventilatory and cardiac function disorders.[1]

The etiology of PPHN is multifactorial. It is most commonly associated with meconium aspiration syndrome (MAS) (42%) and idiopathic PPHN (27%), but is also associated with conditions such as congenital diaphragmatic hernia (CDH), perinatal asphyxia, and sepsis.[2,3] The prevalence of PPHN is 1.9/1,000 in term newborns, with a mortality rate of approximately 11%.[2,4]

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Treatment for PPHN includes gentle ventilation strategies, lung recruitment, inhaled nitric oxide (INO) therapy, and intrapulmonary surfactant administration, which all increase survival.[1] However, PPHN persists for prolonged periods in some patients despite treatment, increasing the length of stay in the Neonatal Intensive Care Unit (NICU) and late morbidity and mortality secondary to PPHN.[5] Although the majority of neonatal pulmonary hypertension (PHT) research has focused on PPHN, knowledge gaps remain and core concepts are often neglected. Furthermore, the relative contribution of chronic PHT to adverse clinical outcomes is just beginning to be realized. Medications such as milrinone, sildenafil, prostaglandins, and bosentan have been proposed for neonates and infants with PHT. However, evidence supporting the use of PHT-specific medications in neonatal patients is limited to case reports or their use in other diseases, particularly treatment of PHT in adults.[6]

Prostacyclin, a metabolite of arachidonic acid produced by the vascular endothelium, has potent pulmonary and systemic vasodilator effects as well as platelet anti-aggregating activity.[7] Treprostinil is a prostacyclin analog that has been approved by the US Food and Drug Administration (FDA) for intravenous, continuous subcutaneous, or inhaled administration in adults with PHT.[8] Although treprostinil is also used in level III NICUs, there is limited evidence of its effects in neonatal patients with PPHN.[9]

The NICU at Garrahan Children's Hospital in Buenos Aires has 54 beds and serves as a major referral center for critically ill neonatal patients from across Argentina. The hospital has extensive clinical and surgical subspecialists and offers advanced technologies, including neonatal extracorporeal membrane oxygenation (ECMO), for treating severe PPHN. In 2013, 28 neonatal patients with a diagnosis of PPHN were admitted. Treatments included inhaled nitric oxide (NO) in 17/28 infants (60%) and ECMO in 7/28 infants (25%). The overall mortality rate was 18%.

Based on the effectiveness and safety of treprostinil in older children and adults with PHT, an observational trial was performed with the aim of assessing the effects and tolerability of this drug in neonatal patients with PPHN. Here, we report the results of a prospective study examining the response to treprostinil in neonates with severe PPHN treated at this major national referral center.

Methods

This study was approved by the Garrahan Children's Hospital Institutional Review Board (IRB).

Study Population

The inclusion criteria were neonatal patients with an echocardiographic diagnosis of PHT admitted to the NICU at Garrahan Children's Hospital between June 2014 and February 2016 with severe hypoxemic respiratory failure despite aggressive cardiac and respiratory support over 48 hours or after surgical correction in CDH patients. Written informed consent was obtained from the parents. Severe disease was defined by persistent clinical instability with the requirement of mechanical ventilator support (MVS) with a high fraction of inspired oxygen (FiO2 $>$ 60%), milrinone therapy (0.5 g/kg/min) and INO therapy (20 ppm). Exclusion criteria were premature neonates with gestational age below 34 weeks, major structural heart diseases, congenital anomalies incompatible with life, or a lack of written informed consent or consent to continue with the study from the parents.

Study Design

Consecutive patients who met the inclusion criteria and whose parents consented to the study were managed according to the following protocol (►**Fig. 1**). Treatment was started with intravenous (IV) treprostinil. The drug was prepared in the hospital pharmacy at a physiological solution dilution of 1000 ng/mL. According to the patient's weight, the dose was converted from ng/kg/min to mL/hour by a computer program and delivered though a continuous infusion pump via a venous catheter in an isolated lumen. We recorded clinical and echocardiography data before and after starting treprostinil on randomly selected days. The primary outcome measure was clinical improvement in oxygenation index (OI) after one week of treatment. Secondary assessment measures were drug effects on MVS requirement, mean airway pressure (MAP), and FiO2. Time was calculated from the beginning of treatment until MVS discontinuation, positive airway pressure, supplemental oxygen, INO, inotropic discontinuation, length of stay, requirement of other surgical procedure, and mortality.

Serial biochemical markers reflecting PHT, including B-type natriuretic peptide (BNP) and uric acid, were measured at the initiation of treatment, weekly for one month, and then monthly until discharge: An echocardiogram was performed by the same expert operator before starting the treatment, weekly for one month, and then monthly until discharge. The following echocardiographic parameters were assessed in a standardized form—systolic and diastolic eccentricity index (SEI and DEI), tricuspid annular plane systolic excursion (TAPSE), four-chamber right ventricle diastolic diameter (RVDD), left ventricle systolic and diastolic diameter (LVSD/LVDD), PDA (in mm), prevailing shunt by PDA and persistent foramen ovale, gradient by PAD, and tricuspid insufficiency (TI) amount and gradient. Lastly, drug tolerability was assessed through clinical follow-up, description of adverse events, and measurement of hematological and biochemical parameters of renal and liver function weekly from the beginning of treatment for one month and then monthly until discharge or death.

Treprostinil administration was initiated at 6 ng/kg/min and gradually increased by 3 ng/kg/min every 8 hours up to 21 ng/kg/min (maintenance dose) based on tolerability. Blood pressure (BP) was continuously monitored and the dose was decreased by 3 ng/kg/min if BP decreased below the 50th percentile for patient age. The time varied depending on tolerability. During drug titration, inotropic doses were not increased and boluses of physiologic or other expanding agents were not given to achieve an increase in treprostinil dose.

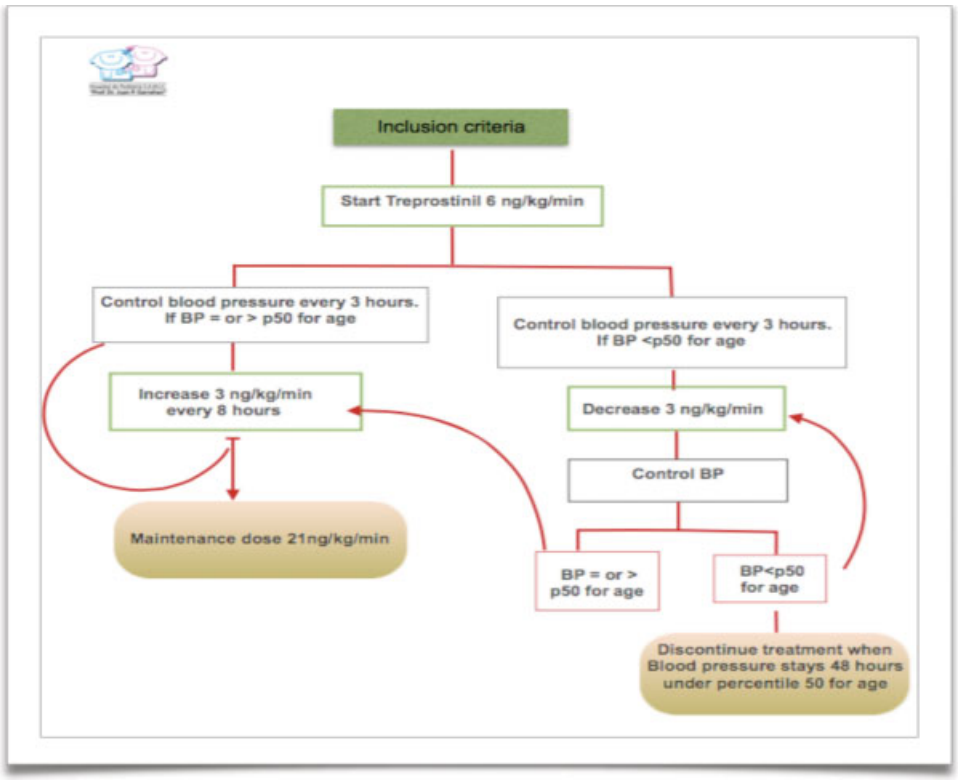

Fig. 1 Treprostinil administration protocol.

IV treprostinil administration was changed to continuous subcutaneous infusion after discontinuation of MVS and inotropic support. In such cases, treprostinil was delivered without dilution at a concentration of 1 mg/mL through a subcutaneous infusion pump (CADD-MS3 Model 7400 Smith Medical ASD, Inc.). The infusion rate was titrated by 0.002 mL/hour and 0.01 mL/hour to maintain a consistent IV dose. Treatment was stopped if the patient's PHT measurements fell below 50% of the systemic pressure by echocardiogram, which was progressively performed for 48 hours.

Data Analysis

We estimated that a sample of 14 patients was needed to detect a difference of 13 points in OI after one week of treatment with a power of 80% and 5% alpha. The patient characteristics and study outcome variables were summarized by means of position measurements and frequency distribution tables, as appropriate. Assessment of pre- to posttreatment changes in the outcome variables were assessed by parametric or nonparametric tests according to the data distribution (Student's *t*-test or Wilcoxon test). Statistical significance was established as $p < 0.05$ with a confidence interval (CI) of 95%. Statistical analysis was performed using STATA SE 12.0 software.

Results

Seventeen consecutive patients met the inclusion criteria and were enrolled in the study. Patient characteristics are summarized in ►**Table 1**.

Table 1 Characteristics of study patients

Variables	Results
Gestational age, week, median (IQR)	37 (37–38)
Birth weight, gram, median, (IQR)	2750 (2500–3200)
C-section	82%
Transfer after birth	64%
Prenatal diagnosis	76%
Cause of PHT	64% CDH left 23% CDH right11% MAS
Severity of CDH Surgical classification[a]	0% type A 13% type B 67% type C 20% type D
Patients that required ECMO before treprostinil treatment	29%
Days of life at CDH surgery, day, median, (IQR)	8 (6–9)
Days of life at the beginning of treprostinil treatment, day, median, (IQR)	17 (13–21)

Abbreviations: CDH, congenital diaphragmatic hernia; PHT, pulmonary hypertension; ECMO, extracorporeal membrane oxygenation.
Note: Data are presented as n (%) unless otherwise stated.
[a]Categorization of severity of disease based on the size of defect on intraoperative findings. The four classifications range from small defects which could be repaired primarily (A) to total diaphragmatic agenesis (D).[26]

Clinical and Echocardiographic Status before IV Treprostinil Treatment

Prior to treatment, all patients were critically ill and required MVS with a median MAP of 14 (interquartile range [IQR]: 13–17) and FiO2 80% (IQR: 60%–100%). The median OI was 20 (IQR: 12–27). All patients were receiving INO and milrinone at 0.5 ng/kg/min and 88% were on inotropic support with dopamine or adrenaline. The median vasoactive-inotropic score was 13 (5–17),[10] the median BNP level was 4724 pg/mL (IQR: 2369–8341 pg/mL), and median uric acid was 1.2 mg/dL (0.8–1.8 mg/dL).

On echocardiogram, 8/17 patients showed an estimated suprasystemic PHT with shunt from the right-to-left through the PDA. The remaining nine patients presented with systemic PHT with bidirectional shunt through the PDA and minimal or no gradient.

Characteristics According to Treatment Received

Treprostinil was initiated at a median age of 17 days of life (IQR: 13–21 days) at a dose of 6 ng/kg/minute and was progressively increased to reach the pre-established therapeutic dose (21 ng/kg/minute) between 48 and 72 hours.

Median treatment time was 61 days (IQR: 38–80 days), of which 21 days (IQR: 14–30) were by intravenous administration. 12/17 of patients changed to subcutaneous infusion with a median usage time of 38 days (IQR: 0–50 days) (►**Fig. 2**).

Treprostinil treatment was suspended in all patients before discharge. Treatment was gradually decreased until suspension when patients were hemodynamically stable without inotropic or MV requirements and showed less than 50% of PHT by echocardiogram. We monitored weaning clinically and by echocardiography, which was progressively performed over 48 hours. After treprostinil discontinuation in 9/17 patients, oral sildenafil was initiated by a cardiologist's indication. We preferred to discharge patients on oral medication on account of the low educational level of their families. No patients had to go back on the previous medication. After discharge they were close monitored by a specific PH follow-up program.

Changes at One Week of Treatment

Fifteen of the 17 study patients were alive at one week of treatment. Of these, 13/15 continued on MVS with a median MAP of 11.8 (IQR: 8–13, $p = 0.0577$) and FiO2 53% (IQR: 40%–67%, $p = 0.0130$), and 2/15 were on noninvasive ventilation (NIV). At one week of treatment, the median OI value was 8 (IQR: 5–12, $p = 0.0089$ vs. pretreatment value). ►**Fig. 3** illustrates the reduction in OI values during treatment with treprostinil.

At one week of treatment, 4/15 of patients continued INO at 5 PPM, 10/15 continued milrinone, and 1/15 continued dopamine. ►**Table 2** presents the basal clinical values at this time.

Regarding laboratory data, there were no statistically significant changes in the median values of BNP (2514.5 pg/mL at one week of treatment, IQR: 1238–7437 pg/mL, $p = 0.5525$ vs. pretreatment value) or uric acid (1.6 mg/dL at one week of treatment, IQR: 0.8–2.2 mg/dL, $p = 0.1217$ vs. pretreatment value). On echocardiogram, 3/15 patients continued to show suprasystemic estimated PHT, 9//15 showed systemic, and 3/15 showed PHT 80% of systemic pressure.

Changes during Treatment until Discharge

The observed changes in biochemical and echocardiographic variables across the treatment period are summarized in ►**Table 3** and **4**. ►**Table 5** shows the clinical outcomes of patients from the beginning of treatment with treprostinil until discharge, as described by means of the median time for treatment discontinuation.

The median length of hospital stay was 94 days (IQR: 80–150). Fourteen patients were discharged. Of these, 3/14 were discharged receiving oxygen via low-flow nasal cannula and 4/14 continued oral sildenafil.

Mortality

Of the 17 patients, 3 (17.6%) died during the study period. Two died within the first few days of treatment (days 2 and 4). On day 14, one patient was discontinued due to a lack of response and progressive hemodynamic impairment and died 27 days later. The causes of death were complications related to PHT with refractory hypoxemia and hemodynamic impairment.

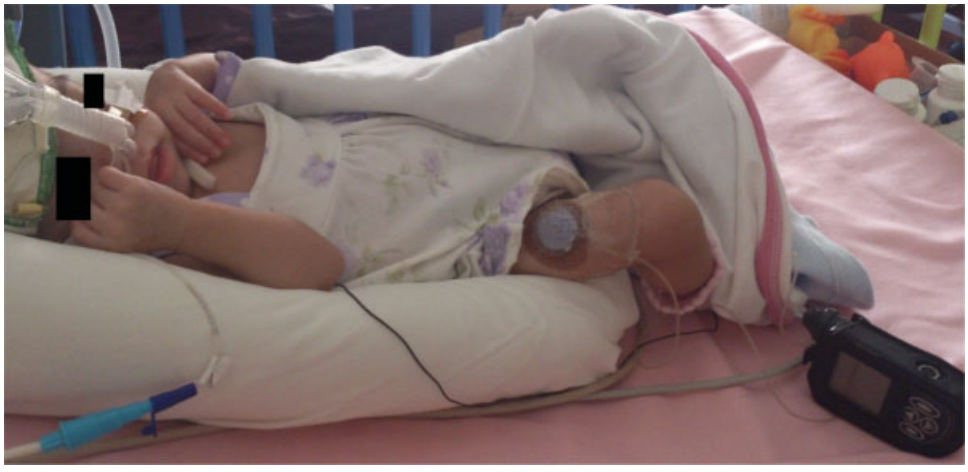

Fig. 2 Patient receiving treprostinil with subcutaneous infusion pump.

Fig. 3 Reduction in oxygenation index (OI) values during treatment with treprostinil.

Table 2 Changes from the beginning up to one week of treatment with treprostinil

	Beginning of the treatment	After one week of treatment	*p*-Value
Patients alive	17	15	
In MVS	17	13	
Median MAP (IQR)	14 (13–17)	11.8 (8–13)	0.057
Median FiO2 (IQR)	80% (60%–80%)	53% (40%–68%)	0.013
Median OI (IQR)	**20 (12–27)**	**8 (5–12)**	**0.008**
INO	17	4	
Milrinone	17	10	
Dopamine	15	1	
BNP pg/ml, median value (IQR)	4724 (2369–8341)	2514.5 (1238–7437)	0.552
Uric acid mg/dL, median value (IQR)	1.2 (0.8–1.8)	1.6 (0.8–2.2)	0.121
Echocardiogram	47% suprasystemic PHT 53% systemic PHT	20% suprasystemic PHT 60% systemic PHT 20% PHT 80% of systemic pressure	

Abbreviations: MVS, mechanical ventilator support; MAP, mean airway pressure; OI, oxygenation index; INO, inhaled nitric oxide; BNP, B-type natriuretic peptide.

Table 3 Changes in biochemical variables

	Basal mean (CI 95%)	1 week mean (CI 95%)	2 weeks mean (CI 95%)	3 weeks mean (CI 95%)	1 month mean (CI 95%)	2 months mean (CI 95%)	3 months mean (CI 95%)
BNP pg/mL	**6305** (1704–8683)	**5194** (1704–8683)	**2830** (1609–4051)	**3015** (1426–4604)	**3010** (1309–4710)	**2219** (678–5118)	**354** (43–665)
Uric acid mg/dL	**1.38** (1.03–1.72)	**1.60** (1.09–2.10)	**1.38** (0.94–1.82)	**1.82** (0.67–2.98)	**1.85** (0.66–3.05)	**2.6** (1.4–3.1)	**2.28** (2.28–2.66)

Drug Tolerance

Mild hypotension in the first 72 hours after starting treatment was observed in 7/17 of patients. During this period, continuous monitoring of BP was performed. During dose titration, if the patient showed minimum modification of the previous BP value, the dose was quickly reduced to the previous level. This was sufficient in all cases to restore normal values with no need for volume expansion or inotropic rising. In those cases, after BP value returned to normal, the dose was increased slower than in the previous phase.

Additional adverse effects included two cases of hematoma at the infusion site of subcutaneous treprostinil, four cases of thrombocytopenia (platelets $<80.000/mm^3$) transient, and two cases of sepsis due to Gram+ bacteria. During

Table 4 Changes in echocardiographic variables

	Basal mean (CI 95%)	1 week mean (CI 95%)	2 weeks mean (CI 95%)	1 month mean (CI 95%)	2 months mean (CI 95%)	3 months mean (CI 95%)
DEI	**1.35** (1.20–1.50)	**1.28** (1.13–1.43)	**1.17** (1.06–1.27)	**1.18** (1.02–1.33)	**1.05** (1.01–1.10)	**1.05** (0.97–1.13)
SEI	**1.43** (1.26–1.61)	**1.39** (1.13–1.65)	**1.31** (1.08–1.54)	**1.25** (1.00–1.49)	**1.06** (1.03–1.09)	**1.09** (0.95–1.23)
TAPSE	**7.62** (6.99–8.24)	**8.40** (7.49–9.32)	**9.21** (88.20–10.16)	**10.83** (9.32–12.34)	**11.77** (10.20–13.20)	**11.72** (10.56–12.89)
RVDD mm	**14.78** (13.11–16.40)	**15.93** (14.07–17.80)	**16.19** (14.44–17.93)	**16.38** (14.60–18.16)	**15.2** (13.58–16.81)	**15.38** (12.27–18.49)
TI GRADE mm hg	**66.22** (54.16–78.27)	**50.11** (40.80–59.41)	**43.87** (32.32–55.42)	**39.28** (24.86–53.70)	**32.00** (22.79–41.20)	
LV-DD mm	**16.06** (14.17–17.96)	**17.92** (15.65–20.19)	**19.73** (17.72–21.74)	**21.30** (19.49–23.12)	**21.18** (19.44–22.91)	**23.22** (19.9–26.48)
LV-SD mm	**9.35** (8.12-10.58)	**10.35** (8.43–12.26)	**11.98** (10.29–13.66)	**11.73** (9.29–14.18)	**12.7** (11.14–14.25)	**14.08** (11.52–16.64)

Abbreviations: DEI, diastolic eccentricity index; SEI, systolic eccentricity index; TAPSE, tricuspid annular plane systolic excursion; RVDD, right ventricle diastolic diameter; LV-DD, left ventricle diastolic diameter; LV-SD, left ventricle systolic diameter.

Table 5 Time to treatment discontinuation

Variables	Results
MVS, day, median (IQR)	18 (8–18)
Positive airway pressure (PAP), day, median (IQR)	19.5 (8–34)
Supplementary O2 by low-flow nasal cannula, day, median (IQR)	32 (16–62)
INO, day, median (IQR)	4 (3–7)
Dopamine, day, median (IQR)	4 (0–8)
Milrinone, day, median (IQR)	8 (4–15)
Parenteral nutrition, day, median (IQR)	18 (10–28)

Note: Data are presented as *n* (%) unless otherwise stated.

the treatment period, hydrothorax was reported in 4/17 patients, pneumothorax in 7/17, and deep venous thrombosis in 10/17. Four of 17 patients underwent surgical PDA closure between 1 month and 45 days of treatment due to symptomatic pulmonary overperfusion.

Discussion

In our patient cohort, the causes of PHT differed from those reported in other intensive therapies.[2,3] The study hospital admits complex congenital pathologies from all over the country and only patients referred from the diagnosis and fetal treatment program at high risk to be transferred were born in the hospital, which is likely why pathologies such as idiopathic PPHN, MAS, and perinatal asphyxia were not reported with the usual frequencies.

In CDH the etiology of PHT is typically multifactorial with some degree of elevated pulmonary vascular resistance that could be acutely reversible and some degree due to fixed resistance secondary to the underlying pulmonary vascular hypoplasia. The potential vasodilatory activity and reversal of remodeling that occurs in the pulmonary vascular wall provide the rationale for prostacyclin therapy for treating PHT in both etiologies.[11] In this study, we used OI to determinate the severity of PHT as a way of measuring the acute effect of treprostinil. OI is an accurate indicator of disease severity at the time of measurement.[12] BNP and echocardiographic findings can evaluate possible changes related to endothelial repair and new vessel formation that would take longer to evidentiate.[13]

Lusk et al reported that 28% of patients with PHT diagnosed by echocardiography at 4 weeks of life died, and the remaining 37% developed chronic lung disease.[14] Medication for such patients is limited. When a baby cannot wean off MVS, INO, or other therapies, treatment with prostanoids can be considered.[15]

Mortality in this cohort of patients was the same as that reported in 2013 at the same NICU before the use of treprostinil. However, in the survival group, patients that started treatment with treprostinil became hemodynamically stabilized, resulting in rapid clinical improvement.

Decreases in MVS requirements (from reduction of OI), inotropic therapies, and INO were the first responses detected during the one week of treatment. Treprostinil infusion was associated with improvement in oxygenation and hemodynamics. Starting at the second week of treatment, improvement was seen in echocardiographic findings. Initially, right-to-left shunting became bidirectional or predominantly left-to-right, which was followed by spontaneous closure of the PDA in 10/14 patients, a decrease in the amount and gradient of TI, and an increase in TAPSE. After one month of therapy, there were significant changes in ventricular sizes.

High uric acid levels in blood are common in patients with PHT and are believed to be secondary to ischemia and tissue

hypoxia as well as to remodeling of the pulmonary vasculature.[16,17] In our cohort, uric acid values remain slightly elevated, but without significant changes, even at hospital discharge.

BNP is a cardiac peptide released by the heart ventricles in response to changes in ventricular pressure and/or volume. Newborns have very variable and abnormally high BNP values due to transitional changes, which decrease to near adult levels by 3 months of life in healthy infants.[18] By contrast, a recently published study conducted in our unit showed that BNP values increased significantly in patients with hemodynamic disorders.[19] Is useful regardless of concomitant inotropic use.[18] In patients with PHT and CDH, BNP is a strong predictor of clinical outcome.[12–20] BNP levels are known to correlate with the gradient of the tricuspid regurgitation jet and the ratio of tricuspid regurgitation jet gradient to mean BP. Further, BNP is weakly correlated with OI.[18] In the present cohort, mean BNP values were very high at the beginning of treatment and matched with patient's PHT, decreased slowly over time, and showed a significant decrease after three months of treatment. Other echocardiographic parameters are known to take time to show a significant change. We thus hypothesize that biomarkers and echocardiographic parameters for evaluating possible changes related to endothelial repair and new vessel formation would take a longer time to evidentiate.[13]

Treprostinil proved to be well tolerated in this cohort of severely ill newborns. Regarding adverse events associated with this medication, the frequency of mild hypotension in the first 48 hours of treatment confirmed the need for progressive increase of the dose to be used. There is no standard protocol for intravenous treprostinil dose escalation; rapid uptitration in inpatient settings provides an opportunity for aggressive treatment in patients with life-threatening status.[21,22] In our cohort, patients did not require volume expansion or inotropic increase during the initiation of treprostinil treatment. Cases of mild hypotension were rapidly reversed when the dose of treprostinil was reduced and then slowly titrated.

Thrombocytopenia has been reported as a treatment related event.[23] In our cohort of patients thrombocytopenia was a transient laboratory finding that resolved in all cases. The appearance of hematoma at the subcutaneous infusion site in two of our cases supports the need for monitoring and monthly changes in the device location.[24] Other adverse effects reported in adult patients with PH receiving treprostinil include pain at the infusion site, headache, diarrhea, and flushing.[25] Although it is difficult to corroborate these effects in neonates, switching from intravenous to subcutaneous infusion did not require increased analgesia dose or suspension of the enteric route. Related to the severity of the underling pathology hydrothorax, pneumothorax and deep venous thrombosis were reported in some of our patients during treprostenil treatment. Furthermore, the drug was not suspended due to adverse events in any of our neonatal patients.

Conclusion

In a cohort of neonatal patients with severe PPHN, treprostinil was well tolerated and induced a degree of hemodynamic stability that allowed rapid improvement of clinical parameters in most cases. Although there was no decrease in mortality in this patient group relative to historic controls, this could be due to the fact that severe CDH cases in the past were more likely to have died before being able to access treatment. The stability of the drug allowed prolonged intravenous and subcutaneous infusion. The latter method was very well tolerated by newborns and reduces the risks of prolonged intravenous infusions.

This study has generated new hypotheses that should be addressed through future work. For example, when is the best time to start this medication in patients with severe PHT? Does this change the mortality results? What patients are nonresponders? What group of pathologies would benefit most from this treatment?

Conflict of Interest
None declared.

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