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Safety, efficacy and Management of subcutaneous treprostinil infusions in the treatment of severe pediatric pulmonary hypertension

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ABSTRACT

Background: Continuous intravenous epoprostenol was the first treatment approved for pulmonary arterial hypertension (PAH) but administration through a central venous line carries risks of thrombosis and sepsis, particularly in children. We sought to evaluate the safety, efficacy and management of subcutaneous (SC) treprostinil in children with PAH.
Methods: Fifty-six children (median age 65, range 1–200 months) were treated with SC treprostinil. Clinical status, echocardiography, NT-proBNP, and site pain and infection were evaluated. Right heart catheterization was performed in 54 patients before starting SC treprostinil infusion and was repeated at 6 months in 31 patients.
Results: Treatment was well tolerated in 79% of patients. Site pain resistant to simple analgesics occurred in 12 patients (21%), but could be managed in 9/12 children. At 6 months, 3 patients had died, 4 had received a Potts shunt and 1 underwent lung transplantation. Among the 48 treated patients, 40 (83%) showed significant improvement in WHO functional class, 6 minute walk distance, NT-proBNP and pulmonary vascular resistance ($p < 0.01$ for all parameters). At last follow-up (median 37 months), ten patients had died, 2 underwent a lung transplantation and 8 underwent a Potts shunt. In 30 of the 36 remaining treated patients, improvement of clinical status was sustained. No children developed sepsis and 12 had minor site infections.
Conclusion: Subcutaneous treprostinil infusion is an effective therapy without serious side effects in children with PAH. Site pain can be managed with simple analgesics in most children.

1. Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by progressive pulmonary vasculopathy [1]. Severe PAH is treated with epoprostenol continuously infused through a central venous catheter [2–6]. In infants and children, complications of long-term intravenous infusions have been reported in up to 60% of patients [7,8]. Frequent inhalations, bronchoconstriction, inadequate fluctuating blood levels and the inability of young children to coordinate the use of the delivery device limit use of inhaled prostanoids [9]. Subcutaneous treprostinil results in equipotent drug levels as intravenous drug delivery [10–12]. The major drawback of SC treprostinil therapy has been infusion site pain. Changes in the management of SC trepostinil therapy have resulted in a renewed interest in SC therapy [13,14]. There remains a paucity of information to inform the management of continuous SC treprostinil infusions in infants and children despite recent favorable single center case series reports [13–16]. Therefore, we sought to describe the efficacy, tolerability and clinical management from a multicenter review of children treated with continuous SC treprostinil infusions.

2. Methods

We undertook a four-center retrospective cohort study conducted with Research Ethics Board approval. We reviewed all available clinical, echocardiographic and hemodynamic data on children with PAH who were treated with a continuous SC infusion of treprostinil between 2009 and 16.

We defined pulmonary arterial hypertension as a mean pulmonary arterial pressure ≥25 mm Hg and a pulmonary arterial wedge pressure <15 mm Hg according to internationally defined criteria for children [17].

Abbreviations: ERA, endothelin receptor antagonist; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; SC, subcutaneous; 6MWT, 6-minute walk test.

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2.1. Patient characteristics

We diagnosed 23 patients with idiopathic PAH, 13 with heritable PAH (4 BMPR2 mutation, 3 TBX4 mutation, 2 ALK1 mutation, one EIF2KF4 and 3 familial PAH without known mutation), 20 patients with PAH associated with a congenital heart defect (one Eisenmenger, 4 left-to-right shunt but PVRI >8 WUm^2, 7 small shunt (Qp:Qs ≤1.3:1) and 8 post-operative PAH), 17 patients with pulmonary hypertension associated with lung disease (10 with broncho-pulmonary dysplasia, and 7 with congenital diaphragmatic hernia) and 3 patients in group 5 of the Nice classification (Table 1). Only the 56 group 1 PH patients were considered for this study.

Fifty-four patients underwent cardiac catheterization at diagnosis. Two patients were considered too sick and were diagnosed by echocardiography alone. All patients were in WHO-FC III-IV at initiation of SC treprostinil except 4 stable patients in FC II who were switched from IV to SC prostanoids.

First line therapy was either bosentan (2 mg/kg b.i.d) ($n = 13$) or sildenafil (1 to 2 mg/kg t.i.d) ($n = 20$) or both ($n = 16$) or triple therapy with SC treprostinil ($n = 7$) according to PAH treatment algorithm [18]. The interval between PAH diagnosis and starting SC treprostinil was 39.3 ± 43 months (range 0–151 months).

We began SC treprostinil administration through a subcutaneously inserted catheter in hospital. Families and children, if developmentally able to do so, were taught how to mix the drug, insert the cannula, prime, run and change doses on the pump. The SC sites used were the outer thigh, the abdomen and the posterior upper arm. We used Cleo (Smiths Medical), or the Silhouette (Medtronics) SC cannulas and Smiths Medical CADD-MS™ 3 microinfusion pumps. We used treprostinil sodium concentrations of 1, 2.5, 5 and 10 mg/ml. We started the infusion at the lowest dose (1.25 ng/kg/min) deliverable by the pump. The infusion rate was titrated by 0.002 ml/h. We increased the dose every 8–12 h until the patient reported benefit or side effects. Doses were increased by 1.25 to 2.5 ng/kg/min. The average dose was 20 ng/kg/min at hospital discharge. Treprostinil concentrations were adjusted to keep the infusion at the smallest volume. The syringe containing the treprostinil solution was changed every 3 days but the subcutaneous cannula remained in situ providing there was no redness, swelling, drug leakage or crystallization around the insertion site. The syringe of treprostinil was placed in a portable pocket and attached to the waist and the catheter tubing was securely fixed.

If patients were hemodynamically unstable, we started IV prostacyclin or treprostinil, and transitioned to SC treprostinil at an equivalent dose over 24 h. The patients were discharged home, albeit with close telephone contact and visits by the PH clinic staff, once they were stable and the family had attained a good understanding of the pump, cannula insertion technique and drug preparation.

Site pain was evaluated using standard scales of pain adapted to age. Site pain was reported as maximal during the first 2–5 days of starting the infusion at a new site. Redness and tenderness during the first 5 days were not regarded as an indication to change the site and subsided gradually. Site pain was treated individually with cold packs, acetaminophen, non-steroidal anti-inflammatory drugs, anti-histamines, and gabapentin.

SC treprostinil dose was adjusted at outpatient visits or by telephone consultation. Specialized nurses trained in the management of PAH patients provided domiciliary technical assistance.

2.2. Data collection

Study data were collected and managed at the Université Paris Descartes.

Baseline data at time of initiation of triple therapy are shown in Tables 1 and 2.

Table 2
Clinical, hemodynamic and outcome data at initiation of subcutaneously delivered treprostinil therapy, after 6 months and at last follow-up.

	Pre-treatment	6 months	Last follow-up median 37 months
WHO FC I–II	4/56 (7%)	40/48 (83%)****	30/36 (83%)****
WHO FC III–IV	52/56 (93%)	8/48 (17%)	6/36 (17%)
Death		3 (5.3%)	10 (18%)
Potts shunt		4	11[a] (19.6%)
Lung transplantation		1	3 (5.3%)
6MWT (meters)[b]	335 ± 140	448 ± 102****	455 ± 102***
	$n = 39$	$n = 36$	$n = 21$
TAPSE (mm)[b]	15 ± 4	17 ± 4***	19 ± 5***
NT-proBNP[b] ($n = 33$)	3293 ± 142	223 ± 388***	876 ± 340***
Syncope[b]	25 (49%)	2 (6%)****	1 (5%)***
Mean PAP[b] (mm Hg)	63 ± 20	50 ± 28**	
	$n = 52$	$n = 31$	
PVRI (WU ∗ m^2)[b]	16 ± 10	12 ± 10***	
CI (L/min/m^2)[b]	3.7 ± 1.4	3.7 ± 1 ns	
RAP (mm Hg)[b]	7 ± 3	6 ± 2.6 ns	

Abbreviations: WHO FC=World Health Organization Functional Class, 6MWT = 6 min walk test, TAPSE = Tricuspid annular plane systolic excursion, NT-proBNP = N terminal pro brain natriuretic peptide, PAP = pulmonary artery pressure, PVRI = Pulmonary vascular resistance index, CI = Cardiac index, RAP = Right atrial pressure.

[a] Includes 3 deaths.

[b] Comparisons made only in FC III–IV patients (the 4 FCII excluded).

** $p < 0.01$.

*** $p < 0.001$.

**** $p < 0.0001$ vs Pre-SC treprostinil condition using Chi2 or paired t-test analyses with a Bonferroni correction for multiple variables.

During follow-up, efficacy was assessed by evaluation of WHO-FC, 6-minute walk distance, NT-proBNP, and echocardiographic parameters of right ventricular function. Right heart catheterization was repeated at 6 months in 25 children (see Table 2).

Treatment tolerance was evaluated at each visit and between visits by telephone contact with the families. A number of families took photographs of the subcutaneous site with their mobile phones and sent them for review.

2.3. Statistical analysis

Data are presented as mean ± SD or median and range for nonparametric data. Differences in outcome parameters before and after starting SC treprostinil infusions were compared using the paired Student *t*-test or Chi2 analysis when appropriate using XLStat 2014 (Addinsoft, New York, USA). Significance threshold was corrected for multiple variables to $p = 0.005$. Variables not following a normal distribution were log transformed and the normal distribution was then checked before statistical analysis.

Table 1
Characteristics of patients at diagnosis and initiation of subcutaneous treprostinil therapy.

Patients $n = 56$	Total	Female	Male	P value
Sex (F/M)	35/21	35	21	
Age at diagnosis (median)	65 ± 60 months (41)	77 ± 62 months (60)	45 ± 53 months (25)	<0.01
Weight at diagnosis (median)	21 ± 16 kg (15 kg)	23 ± 16 kg (18 kg)	16 ± 17 kg (8.5 kg)	<0.01
IPAH	23	13	10	
aPAH-CHD	20	14	6	
hPAH	13	8	5	
Age in months at SC treprostinil (median)	96.8 ± 68 (84)	102.8 ± 69 (92.8)	86.6 ± 68 (66)	NS
Interval (months) between diagnosis and SC treprostinil	39.3 ± 43	34.8 ± 34	46.6 ± 54	NS
WHO FC (I–II/III–IV)%	7%/93%	6%/94%	10%/90%	
Syncope	25	17	8	
Increased NT-proBNP[a]	33	21	12	
Mean PAP mm Hg[b]	63 ± 20	66 ± 20	59 ± 21	NS
PVRI Wood U·m^2	16 ± 10 (15)	18 ± 11 (15.6)	13 ± 7 (12)	<0.01
Cardiac Index L/min/m^2	3.7 ± 1.4	3.6 ± 1.4	3.9 ± 1.5	NS
RAP mm Hg	7 ± 3	7.7 ± 3	5.1 ± 2.5	NS

Abbreviations: F = female, M = male, IPAH = Idiopathic pulmonary arterial hypertension, aPAH-CHD = pulmonary arterial hypertension associated with congenital heart disease, hPAH = heritable pulmonary arterial hypertension, PHT = pulmonary hypertension, BPD = bronchopulmonary dysplasia, CDH = congenital diaphragmatic hernia, SC = subcutaneous, FC = Functional class, NT-proBNP = N terminal pro brain natriuretic peptide, PAP = pulmonary artery pressure, PVRI = pulmonary vascular resistance indexed to body surface area, RAP = right atrial pressure.

[a] Measurements obtained in 51/56 and increased in 33.

[b] 54/56 underwent heart catheterization before SC treprostinil initiation.

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