Pharmacokinetics of treprostinil in children with functional single-ventricle pulmonary arterial hypertension: a randomized controlled trial

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Background: Application of Treprostinil (TRE) in the patients with single ventricle (SV) physiology is very limited, and the optimal dose for children has not been determined. In this study, we aimed to analyze plasma samples to assess the attainment of clinically therapeutic concentrations of TRE and its efficacy and safety in the treatment of pediatric functional SV pulmonary arterial hypertension (FSV-PAH)..

Methods: Pediatric patients with FSV-PAH were recruited in this study. IV TRE at an initial rate of 5 ng/kg/min was administered through the femoral vein with an increase in rate to 10 ng/kg/min every 30 min until the aiming dose of 80 ng/kg/min had been reached. The drug was gradually discontinued after 12 h of treatment at a stable dose. The mean postoperative pulmonary artery pressure (mPAP), pulmonary-to-systemic arterial pressure ratio (Pp/Ps), and the ratio between arterial oxygen partial pressure and inhaled oxygen concentration (PaO_2/FiO_2) were used to evaluate the efficacy of TRE treatment. A multiple linear regression model was used to explore the relevant factors associated with TRE blood concentration.

Results: A total of eight patients were enrolled in the investigation, with an age range of 2.5–9.9 years. The median stable dose of TRE was 70 ng/kg/min with a range of 55–75 ng/kg/min. The median subliminal dose was 55 ng/kg/min with a range of 25–75 ng/kg/min. A linear relationship was established between the TRE dose and the plasma concentration. TRE blood concentrations were associated with dose and patient height. After TRE treatment, mPAP, Pp/Ps, and PaO_2/FiO_2 were significantly improved ($P<0.05$).

Conclusions: A linear relationship was found between the blood concentration of TRE and its dose. IV TRE was an effective therapy without serious side effects in pediatric patients with FSV-PAH.

Trial Registration: ClinicalTrials.gov Identifier: NCT02865733.

Keywords: Single ventricle; pulmonary hypertension; treprostinil; pharmacokinetics

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Introduction

Congenital heart disease (CHD) is one of the most common types of major congenital malformations and is the leading cause of mortality from birth defects (1). According to ESC 2020, the prevalence of CHD worldwide is ~9 per 1,000 newborns, with substantial geographic variation (2). Single ventricle (SV) CHD is a severe cardiac malformation associated with left or right ventricle underdevelopment, resulting in a single functional ventricular chamber that supplies both the systemic and pulmonary circulations (3). It accounts for up to 3% of all cases of CHD (4). The key determinants of single-ventricle physiology include pulmonary vascular resistance (PVR) and systemic ventricular function (5,6). PVR is considered the main determinant affecting the driving force of the ventricular preload, especially in patients with apparently good ventricular and valve function. Increased PVR leads to functional SV pulmonary arterial hypertension (FSV-PAH) (7). According to the latest ESC guidelines, FSV-PAH falls within group 1 of the PAH classification and needs PAH-directed medical therapy (2). Optimizing PVR from the outset is critical due to its unique physiological cycles. Patients with SV physiology who do not fulfill the classic criteria for PAH (mean pulmonary artery pressure (PAP) >25 mmHg and PVR index >3) were found to be amenable to pulmonary vasodilator therapy (4). Based on the information above, there seems to be a rationale for pulmonary vasodilator therapy in FSV-PAH. However, only scarce clinical evidence exists to guide its application, especially in the early postoperative stage (8). In general, there is no approach currently available to administer oral pulmonary vasodilation in the early postoperative period after Fontan completion. Inhaled nitric oxide (iNO) is mainly used in the ICU and is helpful for patients with acute pulmonary vascular crisis or acute exacerbations of PAH, such as underlying parenchymal lung disease or persistent pulmonary hypertension in the newborn (9). Nevertheless, our previous study on the therapeutic application of iNO in the treatment of FSV-PAH showed that a pulmonary arterial pressure bounce might occur after the withdrawal of iNO (10). More importantly, the recommended ESC guidelines state that the application of iNO has to be supplemented by ventilation, which contradicts the principle of early extubation after Fontan surgery. Thus, a pressing demand exists for intravenous preparations for the treatment of FSV-PAH.

Treprostinil (TRE) is a synthetic analog of prostacyclin approved for the treatment of Group 1 or PAH. It is a direct vasodilator of both pulmonary and systemic vascular beds, thereby reducing pulmonary artery pressure and improving systemic oxygenation (11,12). According to 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension, in severe and/or rapidly progressive PAH, continuous IV epoprostenol or treprostinil therapy should be started without delay (9). Recently, some reports about the TRE in children evaluated the pharmacokinetics (PK) of intravenous (IV) and subcutaneous (SC) TRE in pediatric patients with pulmonary vascular disease (13,14). However, the optimal dose for children has not been determined. In addition, due to the unique physiological mechanism of Fontan circulation, there is no convincing evidence for the efficacy of TRE application. Therefore, in this study, we aimed to analyze plasma samples to assess the attainment of clinically therapeutic concentrations of TRE and its efficacy and safety in the treatment of pediatric FSV-PAH.

We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3188).

Methods

Trial design and study population

The study population was derived from a randomized, parallel, single-blind clinical study registered in ClinicalTrials.gov (NCT02865733). Patients were randomly assigned in a 1:1 ratio receive therapy. In this study, subjects were blinded to during the trial. The following inclusion criteria were applied: (I) patients had FSV and were undergoing the Fontan operation in National Children's Medical Center (Shanghai Children's Medical Center); (II) they had a mean pulmonary arterial pressure (mPAP) greater than 15 mmHg; (III) a transpulmonary pressure (TPG) greater than 6 mmHg; and (IV) their legal guardians agreed to their participation in the study and signed the informed consent form. The exclusion criteria were as follows: (I) severe arrhythmia leading to a low cardiac output syndrome; (II) a platelet count <50,000×10^9/L and obvious bleeding.

Ethical approval

This study was approved by the Ethics Committee of Shanghai Children's Medical Center affiliated with Shanghai

Jiao Tong University School of Medicine (approval number: SCMCIRB-K201538). The protocol was conducted in accordance with good clinical practice and the Helsinki Declaration (as revised in 2013). After receiving oral and written explanations of the study, the subjects' legal guardians gave written informed consent before starting the study.

Intervention

Patients were intravenously administered TRE at an initial rate of 5 ng/kg/min through the femoral vein, increasing to 10 ng/kg/min every 30 min until 80 ng/kg/min was reached. Finally, the drug was gradually discontinued after 12 h of treatment at a stable dose. The primary outcome is TRE effects, including pulmonary-to-systemic vascular pressure ratio (Pp/Ps), mean postoperative pulmonary arterial pressure (mPAP) and the oxygenation index (PaO_2/FiO_2). We defined the subliminal dose as the dosage when Pp/Ps decreased by 10%, and a stable dose as the dose at which the nadir occurred. The hemodynamic indicators of all patients were monitored to obtain mPAP and Pp/Ps. In addition, PaO_2/FiO_2 and the positive inotropic drug score (IS) were calculated.

The following formula was used to calculate the dilution concentration of TRE:

$$Dilution\ concentration(mg/mL) = \frac{Dose(ng/kg/\min) * 0.00006}{Intraveous\ \inf usion\ rate(mL/h)} \quad [1]$$

Blood sample collection and analysis

Blood samples were drawn from an intravenous cannula at the following time points: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 16.5 h, and at 2 and 4 h after TRE withdrawal. At each time point, approximately 2 mL of blood was collected from each subject into K3-EDTA tubes and centrifuged at 4 ℃ for 15 min at 3,000 ×g (15). Then, 1 mL of frozen plasma was shipped on solid carbon dioxide (Drikold) to an analytical laboratory (Pharmaceutical Molecular Laboratory, Fudan University, Shanghai, China). An Api-3000 Mass Spectrometer (Applied Biosystems, Foster City, CAUSA), an ANASTAR analyst (version 1.4.1, Applied Biosystems, USA), and an HP 1100 high-performance liquid chromatograph (Agilent Technologies, Palo Alto, CA, USA) were used in the analyses. TRE concentrations were measured using a liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Statistical analyses

The results are expressed as mean ± standard deviations or interquartile range. Correlation analysis was used to assess the relationship between dose and concentration. A multiple linear regression analysis with a stepwise approach was used to examine the association of demographic, dose, and clinical data with TRE blood concentrations. TRE blood concentration was taken as the dependent variable, and background factors (age, height, body surface area), peritoneal dialysis data, hepatic, and renal functions were taken as the independent variables. A stepwise method was used where a variable was entered into the model if the significance level of its F value was less than 0.05 and removed if the significance level was greater than 0.10. A coefficient of determination (R^2) was calculated, which measures how well a model fits the data. Paired *t*-tests were employed to compare the pre- and post-treatment efficacy. Statistical significance was set at $P<0.05$.

Results

Patient characteristics

A total of 40 patients were recruited from the National Children's Medical Center (Shanghai Children's Medical Center) between August 2016 and August 2019. Thirty-six patients were randomized. Twelve agreed to undergo PK monitoring, including eight in the intervention group and four in the control group (*Figure 1*). The PK test was completed in eight patients (six males and two females). Patient characteristics are shown in *Table 1*. The main laboratory test results pre- and post-TRE treatment are shown in *Table 2*.

Treprostinil concentrations

The PK of TRE appeared to be approximately linear in the dose range 5–80 ng/kg/min, and the corresponding blood concentration was about 0.05–21.7 ng/mL (*Figure 2*). Based on the Pp/Ps values, the subliminal dose range was 25–75 ng/kg/min, and the average dose was 52.5±16.69 ng/kg/min. The stable dose range of patients was 55–75 ng/kg/min with an average dose of 65.00±7.07 ng/kg/min. In the corresponding blood conc/min, the drug concentration was 1.1–22.6 ng/mL after 12 h (*Table 3*).

Moreover, the drug concentration was determined within the range 0.32–13.5 ng/mL after 2 h of drug withdrawal

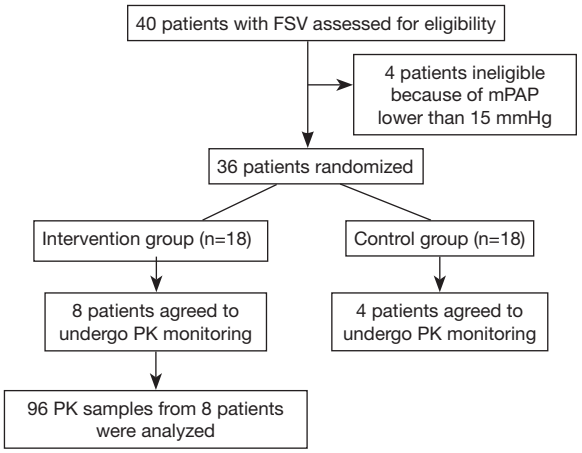

Figure 1 Study profile. FSV, function single ventricle; PK, pharmacokinetics.

and 0.08–4.66 ng/mL after 4 h of drug withdrawal (*Table 3*). The mean plasma concentration-time curves after the application of single doses are presented in *Figure 3*. Results from the multiple linear regression model indicated that TRE blood concentration was associated with dose and height (adjusted R^2=0.802; P<0.001) (*Table 4*). These two factors appear to explain 80.2% of the observed variance in concentration.

Therapeutic effects

The duration of continuous medication ranged from 22.5 to 48.5 h, and the mean duration of medication was 40.18±8 h. Of note, 4 h after drug withdrawal, mPAP (15.38±3.5 *vs.* 18.63±3.66, P=0.021) and Pp/Ps (0.22±0.06 *vs.* 0.35±0.11,

Table 1 Demographic information

Case	1	2	3	4	5	6	7	8
Race	Asian	Asian	Asian	Asian	Asian	Asian	Asian	Asian
Sex	M	M	M	M	F	M	M	F
Age (years)	9.9	3.3	3.4	3.3	3.3	3.1	2.5	2.5
Weight (kg)	37	14.6	14	14.5	14.2	13.7	11	15.8
Height (cm)	145	99	100	90	101	92	86	92
Body surface area	1.21	0.64	0.64	0.58	0.65	0.58	0.51	0.61
Diagnosis	DORV	TA	SV	DORV	TGA	TA	TA	SV
SpO_2 (%)	71	80	89	85	80	70	90	81
mPAP (mmHg)	17	18	19	21	20	15	17	22
Operation (stage)	II	II	II	III	II	III	II	II
Fene	+	/	+	/	+	+	+	+
Peritoneal dialysis	+	/	+	+	/	+	/	+
Concomitant medication[†]	Dopa; Adr; NE	Dopa; Mil	Dopa; Adr; NE; MP	Dopa; Adr; MP	Dopa; Mil; Adr; NE	Dopa; Adr; MP	Dopa; Mil; Adr; MP	Dopa; Mil; Adr; Amio
ICU stay (days)	3	3	7	7	5	6	3	6
T_{MV} (h)	6.5	4.67	23	97	45.63	21.5	4.63	25.5
T_{CD} (days)	9	11	2	16	16	18	6	17
Length of stay (days)	17	14	23	22	20	23	10	22
FB (mL/kg/d)	−11.74	−17.61	−3.83	−5.58	/	1.57	−6.35	−10.01
CD (mL/kg/d)	10	12.33	31.43	16.03	/	29.56	13.64	32.59

[†], concomitant medication during intravenous infusion of treprostinil; +, yes. mPAP, mean pulmonary artery pressure; Fene, fenestration; ICU, intensive care unit; DORV, double outlet right ventricle; TA, tricuspid atresia; SV, single ventricle; TGA, transposition of great arteries; T_{MV}, mechanical ventilation time; T_{CD}, chest drainage time; FB, fluid balance; CD, chest drainage; Dopa, dopamine; Mil, milrinone; Adr, adrenergic; NE, noradrenaline; ISO, isoproterenol; MP, methylprednisolone; Amio, amiodaron.

Table 2 Main laboratory test results before and after intravenous infusion of treprostinil

Case	1	2	3	4	5	6	7	8
Before treatment [normal range]								
WBC ($\times10^9$/L) [4.0–15.0]	4.1	6.4	8.3	17.2	6.3	6.4	9.3	9.9
RBC ($\times10^{12}$/L) [3.7–5.8]	7.1↑	5.91↑	5.2	6.14↑	5.66	5.7	5.43	5.2
HB (g/L) [110–160]	219↑	175↑	149	179↑	160	169↑	151	158
N% [50–70]	61.6	52.0	49.5↓	59.7	54	46.1↓	42.8↓	22.3↓
L% [20–40]	29.8	37.4	37.2	20.2	35.9	46.1↑	48.4↑	69.1↑
PLT ($\times10^9$/L) [100-–550]	241	222	439	132	/	357	349	356
CREA (μmol/L) [9–88]	42	35	56	11	/	27	31	35
AST (U/L) [15–46]	29	24	34	32	/	41	35	32
ALT (U/L) [13–69]	41	19	18	10	/	20	28	24
CRP (mg/L) [<8]	12↑	/	/	/	<1	<1	<1	<1
NT-proBNP (pg/mL) [0–125]	6	14	66	23	/	349↑	35	30
ROSS Class	I	I	I	I	I	I	I	I
Echo								
Common atrioventricular regurgitation	+ to ++	–	+	–	–	–	–	–
Anastomotic obstruction	–	–	–	–	–	–	–	–
ΔP (mmHg)	/	/	/	/	/	/	58	/
After treatment [normal range]								
WBC ($\times10^9$/L) [4.0–15.0]	15.4↑	8.7	18.1↑	15.2↑	15.9↑	15.8↑	14.4	12.5
RBC ($\times10^{12}$/L) [3.7–5.8]	5.68	4.54	4.44	5.7	4.05	4.7	4.15	3.92
HB (g/L) [110–160]	176↑	132	130	167↑	116	138	120	118
N% [50–70]	87.2↑	59.2	64	73.1↑	81.8↑	81↑	81.5↑	57.4
L% [20–40]	3.4↓	29	26.4	16.9↓	7.5↓	9.2↓	9.8↓	35.5
PLT ($\times10^9$/L) [100–550]	153	106	151	90↓	146	327	208	52↓
CREA (μmol/L) [9–88]	/	/	52	/	41	48	27	42
AST (U/L) [15–46]	/	/	50↑	/	68↑	30	84↑	456↑
ALT (U/L) [13–69]	/	/	11	/	31	7	15	638↑
CRP (mg/L) [<8]	/	50↑	20↑	82↑	65↑	10↑	69↑	11↑
PCT (ng/mL) [<0.5]	/	/	3.53↑	1.4↑	1.24↑	7.94↑	8.95↑	5.62↑
NT-proBNP (pg/mL) [0–125]	240↑	/	/	/	3,700↑	4,000↑	/	1,100↑
SaO_2-SvO_2 (%)	/	14.9	45.8	20.9	34.1	27.5	/	48.6
$PvCO_2$-$PaCO_2$ (mmHg)	/	3.1	13.8	10.7	6.5	6.1	/	12.9
Lac (mmol/L)	0.9	1.1	1.1	1.1	1.4	1.3	0.6	1.2

Table 2 (*continued*)

Table 2 (*continued*)

Case	1	2	3	4	5	6	7	8
Before discharge [normal range]								
WBC ($\times10^9$/L) [4.0–15.0]	7.8	10.4	10.3	8.2	13	10.9	15.7↑	17.1↑
RBC ($\times10^{12}$/L) [3.7–5.8]	4.87	4.69	3.78	5.23	4.16	4.35	5.55	4.17
HB (g/L) [110–160]	154	137	111	152	120	131	158	123
N% [50–70]	75.4↑	55.6	62.6	58.5	68.9	55.6	66.1	60
L% [20–40]	15.6↓	27.5	22.4	27.6	18.9↓	33.2	23.1	34.5
PLT ($\times10^9$/L) [100–550]	116	198	650↑	258	420	178	236	401
CREA (μmol/L) [9–88]	45	/	/	/	18	/	39	32
AST (U/L) [15–46]	27	/	/	/	36	/	34	19
ALT (U/L) [13–69]	45	/	/	/	60	/	19	25
CRP (mg/L) [<8]	12↑	33↑	4	13↑	17↑	5	18↑	<1

Common atrioventricular regurgitation: '+' means mild regurgitation; '++' means moderate regurgitation; '–' means no regurgitation. Anastomose: '–' means patent; '+' means obstruction. WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; N%, percentage of neutrophils; L%, percentage of lymphocytes; PLT, platelet; CREA, creatinine; AST, aspertate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; PCT, procalcitonin; NT-proBNP, N-terminal pro brain natriuretic peptide; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; $PvCO_2$, venous partial carbon dioxide pressure; $PaCO_2$, arterial partial carbon dioxide pressure; Lac, lactic acid.

P=0.002) were lower than the baseline values before the treatment, whereas a significant improvement was observed in PaO_2/FiO_2 (162.29±56.16 *vs.* 102.57±34.3, P=0.028). IS scores did not change (*Table 5*). The days of ICU stay were 5.00±1.41 d, the mechanical ventilation time was 21 [4, 27] h, the chest drainage time was 11.88±5.84 d, and the hospital stay was 18.88±4.79 d.

Adverse effects

No pain or reactions (erythema, sclerosis, or rash) were observed at the infusion site in any of the eight patients. A decrease in platelet count after TRE treatment was observed in all patients. However, the platelet count recovered before discharge in the absence of a platelet transfusion. Therefore, the decrease in platelets was considered to be surgery related. Abnormal increases of AST and ALT were observed in one patient. No serious adverse side effects occurred, including phlebitis, diarrhea, edema, or nausea.

Discussion

TRE was used either as a second-line therapy, added to a phosphodiesterase-5 inhibitor (sildenafil) or an endothelin receptor antagonist (bosentan), or as a third-line therapy, added to a biotherapy with sildenafil and bosentan. Overall, 12 clinical trials on treprostinil for children with PH were registered on the clinical trial registries from the World Health Organization network (16). According to previous reports, TRE therapy is safe and efficacious in pediatric CHD patients with PAH (17-19). Intravenous (IV) or subcutaneous (SC) administration are two available options for continuous TRE use (13). However, both routes have some limitations. TRE IV administration occurs via a central line catheter, but this can be complicated by infection or occlusion. SC administration via a SC catheter can be complicated by pain at the SC infusion site (20). A pharmacokinetics study compared the differences between IV and SC TRE in pediatric patients with pulmonary vascular disease (13). Although blood concentrations per given dose of IV TRE were higher than those per given dose of SC TRE, the difference was not significant (13). As our pediatric patients with FSV-PAH were in a cardiac surgery intensive care unit, we gave priority to IV administration of TRE via a central venous catheter under the best nursing conditions. But to avoid risks such as sepsis and thrombosis caused by long-term TRE administration through a central venous line, SC infusion, or an inhalation

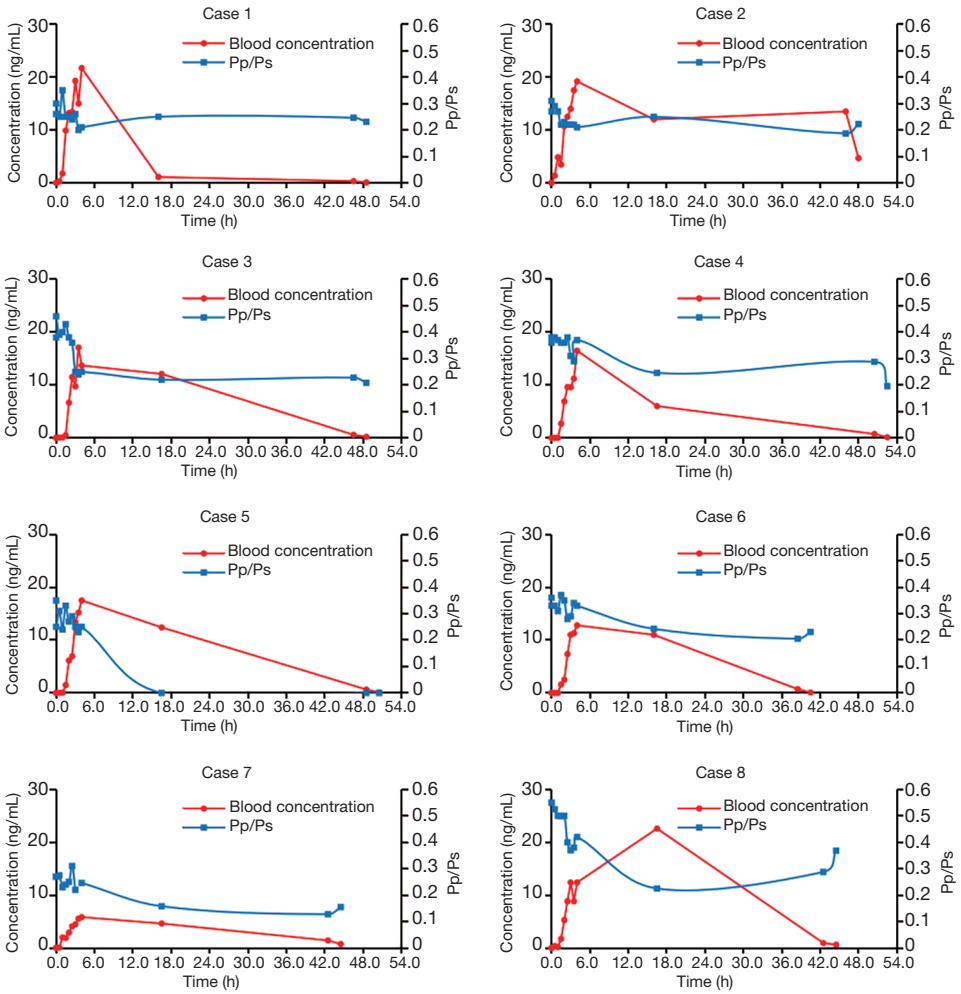

Figure 2 Variation tendency of treprostinil concentration and Pp/Ps, the ratio of the pulmonary arterial pressure to the systemic pressure.

Table 3 Treprostinil concentrations

Case	1	2	3	4	5	6	7	8
D_{sm} (ng/kg/min)	75	25	65	65	45	55	65	55
C_{Dm} (ng/mL)	21.70	19.20	13.70	16.50	17.50	12.80	5.85	12.40
Pp/Ps-$_{Dm}$	0.21	0.21	0.25	0.37	0.27	0.24	0.25	0.42
D_s (ng/kg/min)	70	70	65	75	65	55	65	55
C_s (ng/mL)	1.10	12.00	12.10	6.01	12.40	11.00	4.63	22.6
Pp/Ps_{Ds}	0.25	0.25	0.22	0.25	–	0.24	0.16	0.23
$C_{w\text{-}2h}$ (ng/mL)	0.32	13.50	0.58	0.74	0.65	0.71	1.43	0.95
$C_{w\text{-}4h}$ (ng/mL)	0.08	4.66	0.20	0.12	0.10	0.10	0.75	0.63

D_{sm}, subliminal dose; Pp/Ps, the ratio of the pulmonary arterial pressure to the systemic pressure; D_s, stable dose; D_m, max dosage; C_{Dm}, concentrations at max dosage of treprostinil, which was 80 ng/kg/min; Cs, concentrations at a stable dosage of treprostinil; $C_{w\text{-}2h}$ & $C_{w\text{-}4h}$, concentrations 2 and 4 hours after withdrawal of treprostinil.

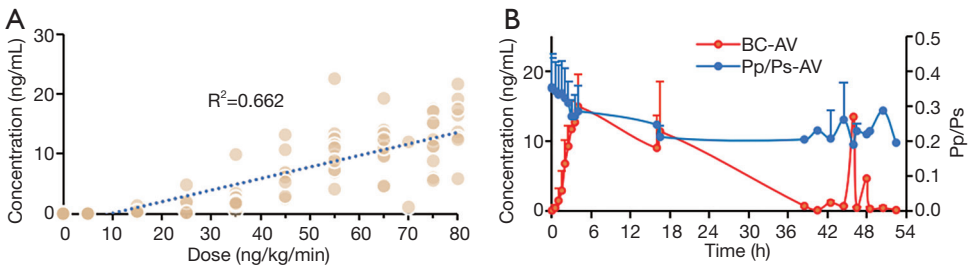

Figure 3 Scatter plot of dose and concentration. (A) The linear relationship between concentration and dose is as follow: Y = 1.76 +0.19 × X. (X: dose; Y: concentration), R^2=0.662. (B) The relationship between blood concentration and Pp/Ps. Pp/Ps, the ratio of the pulmonary arterial pressure to the systemic pressure.

Table 4 Significant factors associated with blood concentration identified by multiple linear regression model

	β	t	P	95% CI	
				Lower limit	Upper limit
Constant	−15.525	−7.354	<0.001	−19.746	−11.303
Dose (ng/kg/min)	0.235	15.332	<0.001	0.205	0.266
Height (cm)	0.113	5.864	<0.001	0.075	0.152

Concentration = −15.525 + 0.235 × dose (ng/kg/min) + 0.113 × height (cm), F=134.73, P<0.001, R^2=0.809, Adjusted R^2=0.802.

Table 5 The therapeutic effect of treprostinil

Index	Before treatment	After treatment
mPAP (mmHg)	18.63±3.66	15.38±3.5*
Pp/Ps	0.35±0.11	0.22±0.06**
P/F (mmHg)	102.57±34.31	162.29±56.16*
IS (score)	9.56±4.66	14.56±9.92

IS = dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 10 × milrinone (μg/kg/min) + 100 × adrenergic (μg/kg/min) + 100 × noradrenaline (μg/kg/min). Treprostinil treatment *vs*. before treatment, *P<0.05, **P<0.01. mPAP, mean pulmonary artery pressure; Pp/Ps, the ratio of the pulmonary arterial pressure to the systemic pressure; P/F, oxygenation index; IS, inotropic drug score.

route might be a better choice for children with PAH (17).

Several studies have reported the therapeutic effect of TRE in pediatric patients with PAH, but documented results of TRE in pediatric patients with FSV-PAH are lacking. The goal dose of TRE was approximately 20 ng/kg/min in many studies (18,21). De Bie *et al.* reported TRE concentrations during clinical treatment in four neonates on extracorporeal membrane oxygenation support (18). The starting dose of TRE was 4 ng/kg/min and was gradually increased by 4 ng/kg/min every 8 hours aiming for a dose of 20 ng/kg/min (18). Finally, TRE doses ranging from 20 to 58 ng/kg/min reached concentrations of 0.99–4.39 ng/mL in these neonates with PAH and resulted in clinical improvement (18). Levy *et al.* found that the average stable dose of SC TRE in children with severe PAH was 55 ng/kg/min with a range of 15–350 ng/kg/min (17). A pharmacokinetic study of oral TRE in pediatric patients with PAH indicated that TRE concentration had a linear relationship to oral TRE dose, and pediatric patients might require a higher oral TRE dose than adults (14). This phenomenon was also observed in pediatric patients who received steady-state IV and SC TRE (13). In this study, we chose 5 ng/kg/min as an initial rate with an increasing rate of 10 ng/kg/min every 30 min up to the aiming dose of 80 ng/kg/min to explore the blood concentration of IV TRE in SV CHD patients undergoing Fontan surgery. The relationship between the concentration and the dose was approximately linear, and the corresponding concentration was 0.05–21.7 ng/mL. The drug concentration reached a relatively stable level at approximately 16 h. Moreover, our results indicated that the subliminal dose range for our patients was 25–75 ng/kg/min, and the final stable dose range was 55–75 ng/kg/min with an average stable dose of 65.00±7.07 ng/kg/min. These doses were higher than the doses determined in previous investigations (14). Our results suggested that pediatric patients with FSV-PAH are more likely to need a higher therapeutic dose of TRE than general PAH patients. To further explore the influencing factors of TRE blood concentration, we used a multiple linear regression analysis with age, height, body surface area, peritoneal dialysis data, hepatic, and renal functions as the independent variables. We found that TRE blood

concentrations were associated with two factors: dose and height. Since the therapeutic dose of TRE was determined by weight in this study, these results from the multiple linear regression model suggest that the use of body surface area to determine the therapeutic dose might be a better choice for pediatric patients with PAH.

The efficacy and safety of TRE were also investigated in this study. A single center retrospective cohort study by Handler *et al.* reported that 17 pediatric patients with SV physiology who received SC TRE demonstrated clinical benefits, with improvements in oxygen saturation, exercise tolerance, and PVR index (19). TRE therapy in children with PAH also showed an improved pulmonary-to-systemic vascular resistance ratio (Rp/Rs) (22), and TRE has been shown to lower the mPAP in patients with PAH (23). Furthermore, add-on therapy with SC TRE had a rescue value in children with refractory PAH (24), and TRE therapy improved symptoms and hemodynamics in pediatric patients with mild PAH awaiting heart transplantation (21). However, the efficacy and safety data of IV TRE in pediatric populations with FSV-PAH are limited. In this study, we found that IV TRE improved mPAP, Pp/Ps, and PaO_2/FiO_2 in children with FSV-PAH. Besides vasodilation, TRE can also inhibit platelet activation (25), and thrombocytopenia is a common side effect during TRE treatment (26). In this study, we also observed a decreased platelet count in all patients after TRE treatment. However, the platelet count recovered before discharge in the absence of a platelet transfusion. Therefore, the decrease in platelets was considered to be surgery related. Although improvements in tissue oxygenation, enhanced cardiac function, and hemodynamic stability were established in our study, further large-sample research is needed to confirm our findings.

Limitations

Certain limitations of this study should be acknowledged. Firstly, because it was hard for patients to accept sparse PK research, the sample size was small, which may have introduced bias. However, in our follow-up study, we're still collecting relevant samples. Therefore, we will continue to report related studies in the future. Secondly, we established that TRE significantly improved mPAP, Pp/Ps, and PaO_2/FiO_2, but further studies are needed to confirm whether it can improve the short-term prognosis of Fontan children. Thirdly, PVRI was not evaluated in our investigation.

Conclusions

In this study, we investigated the PK of IV TRE in children with FSV-PAH. TRE blood concentrations were associated with dose and patient height. A linear relationship was found between the blood concentration of TRE and its dose. The use of body surface area to determine the therapeutic dose of TRE might be a better choice. IV TRE resulted in the improvement of mPAP, Pp/Ps, and PaO_2/FiO_2 in children with FSV-PAH.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Shanghai Children's Medical Center affiliated with Shanghai Jiao Tong University School of Medicine (approval number: SCMCIRB-K201538). The study protocol was conducted in accordance with good clinical practice and the Helsinki Declaration (as revised in 2013). Oral and written

explanations of the benefits and risks of participating in this study were communicated to the participants' legal guardians. Written informed consent from the subjects' legal guardians was obtained before the start of the study.

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