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The effects of standardized intravenous treprostinil in pulmonary arterial hypertension patients after total cavo-pulmonary connection procedure

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Abstract

Objective Total cavo-pulmonary connection (TCPC) is a palliative treatment for single ventricular malformations. For high-risk patients (preoperative mean pulmonary arterial pressure, mPAP > 15 mmHg), between the inhaled and oral targeted medications, the application of intravenous treprostinil as a bridge therapy to achieve "seamless" management is core postoperative treatment. This study intends to explore the effect of different administration regimens on early postoperative recovery.

Methods This was a retrospective cohort study. High-risk pediatric patients (age ≤ 14 years) who underwent TCPC procedure in Fu Wai Hospital from 2015 to 2022 were included. Since the regimen of treprostinil was standardized in our center in 2021, the patients in 2020 and before were included in group 1, patients in 2021 and 2022 were included in group 2. The hemodynamic parameters were compared before and after the maintenance dose of treprostinil. The differences of demographic characteristics, surgical data and postoperative recovery were compared between the two groups.

Results A total of 51 pediatric patients were included. Group 1 included 35 patients who received treprostinil at 1–3 postoperative days and an average dose of 12 ± 4 ng/(kg·min). Group 2 included 16 patients who received treprostinil within postoperative 1 day and an average dose of 22 ± 7 ng/(kg·min). There were no significant differences between the two groups in terms of age, weight, preoperative percutaneous oxygen saturation and mPAP, heterotaxy syndrome, TCPC procedure type, other concurrent procedure, cardiopulmonary bypass time and aortic cross-clamp proportion ($p > 0.05$). After 24 h of treprostinil treatment, the mPAP in group 1 reduced from 17 ± 3 mmHg to 15 ± 2 mmHg ($p < 0.001$), and in group 2 from 17 ± 2 mmHg to 14 ± 2 mmHg ($p < 0.001$), with no difference between groups. In the postoperative recovery, patients in Group 2 exhibited a reduced duration of mechanical ventilation, 19 (11, 25) hours vs 69 (23, 189) hours, $p = 0.001$; a shorter stay in the ICU, 8 (6, 12) days vs 16 (9,26) days, $p = 0.006$; and a shorter postoperative length of stay, 27 (17,55) days vs 39 (29,58) days, $p = 0.032$. Patients in Group 2 also exhibited a lower incidence of thromboembolic events, 0 (0/26) vs 26% (9/35), $p = 0.043$; and the need for renal replacement therapy, 0 (0/26) vs 31% (11/35), $p = 0.011$.

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Conclusion Treprostinil reduces pulmonary artery pressure after TCPC procedure. The standardized application of treprostinil may improve the postoperative recovery which should be proven by randomized controlled trials or matched cohort studies in the future.

Keywords Single ventricle, Pulmonary hypertension, Total cavo-pulmonary connection, Treprostinil

The total cavo-pulmonary connection (TCPC) is a classic palliative surgery for the treatment of single-ventricle anomalies. Pulmonary arterial hypertension (PAH) is one of the common complications of single-ventricle anomalies and is also a key determinant of the success of TCPC surgery [1]. With the gradual improvement in perioperative management, postoperative complications have decreased gradually, leading to a significant improvement in patient prognosis [2]. However, for high-risk patients with concomitant pulmonary hypertension, the surgical prognosis remains unsatisfactory, particularly as early postoperative complications can lead to delayed recovery or even increased risk of mortality. In patients with single-ventricle anomalies, unlike the commonly used criterion of mean pulmonary arterial pressure (mPAP) > 20 mmHg [3], the criterion for single-ventricle-associated PAH is mPAP > 15 mmHg [4].

Due to the lack of pulsatile blood flow in the pulmonary artery post-TCPC surgery, even mild increases in pulmonary artery pressure can lead to a significant reduction in pulmonary circulation. Therefore, the application of targeted PAH medications to reduce pulmonary vascular resistance is essential in the post-TCPC treatment regimen. Currently, numerous studies focus on the specific effects of targeted drug therapy on post-TCPC patients. Goldberg et al. conducted a randomized, double-blind, placebo-controlled crossover study involving 28 patients, demonstrating that oral sildenafil improved ventilatory efficiency during cardiopulmonary exercise testing [5]. Similarly, Rhodes et al. employed the same study design and demonstrated, through a study of 18 patients, that inhaled iloprost improved pulse oxygen saturation and maximal oxygen consumption during cardiopulmonary exercise testing [6]. Hebert et al. conducted a randomized, double-blind, placebo-controlled study involving 74 patients, with 37 receiving oral bosentan treatment and 37 receiving oral placebo for a duration of 14 weeks, demonstrating the ability of bosentan to improve cardiopulmonary exercise capacity, exercise endurance, and functional class [7]. Constantine et al. conducted a retrospective analysis of 1538 patients from 10 hospitals in the UK, of which only 76 (4.9%) received targeted drug therapy. After matching, analysis of 108 patients revealed that targeted drug therapy could improve patients' NYHA functional class [8].

However, these studies still have certain limitations. Primarily, they mainly include patients receiving outpatient medications and follow-up after discharge from surgery, most of whom undergo oral medication therapy. The methods used to evaluate efficacy also tend to focus more on tests of exercise capacity. However, in the early post-TCPC period, due to increased central venous pressure in patients leading to gastrointestinal congestion and poor drug absorption, clinicians often prefer drugs administered via inhalation or intravenous/subcutaneous infusion routes. Moreover, in terms of efficacy, greater attention is placed on the impact on hemodynamics and important postoperative recovery indicators.

Treprostinil is a targeted medication within the prostacyclin pathway and its analogs, which can be administered via intravenous/subcutaneous infusion pumps. Currently, this medication is considered the first-line and essential therapy for patients with severe PAH (WHO functional class III–IV) [9]. For high-risk single-ventricle patients undergoing TCPC surgery, intravenous treprostinil infusion can serve as a bridging therapy between inhaled nitric oxide and oral targeted medications, aiming at achieve seamless management of targeted drug therapy. There are already small-sample self-controlled studies supporting the effectiveness and safety of treprostinil l in high-risk single-ventricle postoperative patients [10, 11]. However, there is a lack of research supporting the timing and maintenance dose of medication administration. This study aims at explore whether standardized timing and dosing of treprostinil administration can further improve hemodynamic status and postoperative recovery indicators in high-risk single-ventricle patients after TCPC surgery, using a retrospective cohort study approach.

Data and methods

Patient inclusion and grouping criteria

This retrospective study analyzed pediatric patients (≤ 14 years old) who underwent TCPC surgery and were hospitalized at Fuwai Hospital from 2015 to 2022. Inclusion criteria: 1. preoperative right heart catheterization showing mPAP > 15 mmHg; 2. postoperative initiation of intravenous treprostinil therapy in the intensive care unit. Exclusion criteria: receipt of extracorporeal membrane oxygenation support postoperatively.

Since our center standardized the use of treprostinil in 2021, patients undergoing surgery from 2015 to 2020 were assigned to Group 1, while patients undergoing surgery in 2021 and 2022 were assigned to Group 2.

Treprostinil and other targeted medication administration strategies

In our center, all high-risk TCPC patients (mPAP > 15 mmHg) were indicated for postoperative use of treprostinil. In those patients, blood pressure stability is initially maintained using vasopressors and fluid therapy. Inhalation of 20 ppm nitric oxide via a ventilator is used to reduce pulmonary vascular resistance, gradually tapering off nitric oxide concentration before planned extubation, and sildenafil (Pfizer Inc., Puerto Rico) is added at a dose of 0.5 mg/kg, up to a maximum of 20 mg per dose, three times daily. Once the patient's blood pressure stabilizes, intravenous treprostinil (Zhaoke Pharmaceutical (Hefei) Co., LTD., China) therapy is initiated. Due to initial limited experience with treprostinil, the starting dose is 4 ng/ (kg·min), with increments every 2 h of 2–4 ng/(kg·min) until the symptom improvement is observed (reduction in central venous pressure, improved fluid intake requirements, gradual resolution of tachycardia), maintaining therapy at the current dose. Since standardization of treprostinil therapy began in 2021, administration starts as soon as circulatory stability is achieved postoperatively, with an initial dose of 5 ng/ (kg·min), increments every 30 min of 5 ng/(kg·min) until reaching the maximum tolerated dose (when blood pressure fluctuates), then transitioning to maintenance therapy. Once gastrointestinal function recovers in all patients, oral medication therapy is initiated, with bosentan (Actelion Pharmaceuticals Ltd., Switzerland) at a dose of 2 mg/kg per dose, up to a maximum of 125 mg per dose, twice daily, in combination with oral sildenafil therapy. Patients continue oral targeted medication therapy after discharge from the intensive care unit. Following initiation of oral targeted medication therapy in pediatric patients, intravenous treprostinil is gradually discontinued without conversion to subcutaneous administration.

Data collection

Data from both groups of pediatric patients were recorded preoperatively, intraoperatively, and postoperatively. Preoperative data primarily included: age, gender, weight, transcutaneous oxygen saturation, hemoglobin concentration, presence of heterotaxy syndrome, and preoperative mPAP. Intraoperative data mainly included: TCPC procedure, whether concomitant atrioventricular valve repair/replacement, pulmonary vein stenosis correction, extracorporeal circulation time, whether aortic clamping was performed, and whether a fenestration was created. Postoperative data mainly included: maintenance dose and duration of treprostinil. Hemodynamic parameters were recorded in both groups of patients before and at 6, 12, 18, and 24 h after initiation of intravenous treprostinil, including: mPAP (superior vena cava pressure) and vasopressor score, where the vasopressor score = dopamine [μg/(kg·min)] + dobutamine [μg/(kg·min)] + milrinone [μg/(kg·min)] × 10 + adrenaline [μg/(kg·min)] × 100 + vasopressin [U/(kg·min)] × 10,000. Other recorded parameters included: duration of mechanical ventilation, length of stay in the intensive care unit, postoperative hospital stay, occurrence of tachyarrhythmias, volume of chest drainage, duration of chest tube placement, occurrence of thromboembolic events, receipt of renal replacement therapy, need for multiple endotracheal intubations, need for tracheostomy, and in-hospital mortality rate. Potential adverse reactions to treprostinil included low blood pressure, pain, diarrhea, and thrombocytopenia.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, USA). The Shapiro–Wilk test was utilized to assess the normality of continuous variables. Normally distributed continuous variables were described as mean ± standard deviation, while non-normally distributed continuous variables were described as median (interquartile range), and categorical variables were described as frequency (percentage). For comparisons of changes in hemodynamic parameters before and after treprostinil infusion and between groups, a one-way repeated measures analysis of variance (ANOVA) was conducted. The assumption of sphericity was assessed using Mauchly's test of sphericity or Greenhouse–Geisser correction as appropriate. Continuous variables between groups were compared using independent samples t-tests or Wilcoxon rank-sum tests depending on the normality of the data distribution. Categorical variables were compared using Chi-square tests, continuity correction, or Fisher's exact test as appropriate. Expectation maximization was utilized to estimate missing values. A significance level of $P \leq 0.05$ was considered statistically significant.

Ethical support

This study has been reviewed and approved by the Ethics Committee of Fuwai Hospital, with ID: 2022–1859. Due to its retrospective nature, informed consent was waived. The ethical principles outlined in the 1964 Helsinki Declaration were adhered to throughout the study.

Results

Out of a total of 829 patients, 53 patients met the inclusion criteria. After excluding 2 patients who received extracorporeal membrane oxygenation support, a total of 51 patients were included. Among them, 35 patients were included in Group 1, initiating maintenance treprostinil therapy within 1–3 days postoperatively, with an average dose of 12 ± 4 ng/(kg·min). Group 2 included 16 patients, starting maintenance treprostinil therapy within 1 day postoperatively, with an average dose of 22 ± 7 ng/(kg·min).

The demographic characteristics of patients in both groups are shown in Table 1, with no statistically significant differences between the two groups ($p > 0.05$). The surgical data of patients in both groups are presented in Table 2, with no statistically significant differences between the two groups ($p > 0.05$).

Regarding hemodynamic changes after treprostinil infusion, the mPAP gradually decreased at each observation point after maintenance infusion in both groups. In Group 1, the mPAP decreased from 17 ± 3 mmHg to 15 ± 2 mmHg ($p < 0.001$), and in Group 2, it decreased from 17 ± 2 mmHg to 14 ± 2 mmHg ($p < 0.001$). However, there was no statistically significant difference in mPAP changes between the two groups ($p = 0.18$). The changes in vasoactive inotropic score in both Group 1 and Group 2 were not statistically significant, and there was no statistically significant difference in changes between the two groups ($p > 0.05$), as shown in Table 3.

Regarding postoperative recovery indicators, patients in Group 2 had significantly shorter mechanical ventilation time compared to those in Group 1 (19 [11, 25] hours vs 69 [23, 189] hours, $p = 0.001$). Similarly, ICU stay (8 [6, 12] days vs 16 [9, 26] days, $p = 0.006$) and postoperative hospital stay (27 [17, 55] days vs 39 [29, 58] days, $p = 0.032$) were shorter in Group 2 compared to Group 1. Additionally, the proportion of patients with thromboembolic events (0 [0/26] vs 26% [9/35], $p = 0.043$) and requiring renal replacement therapy (0 [0/26] vs 31% [11/35], $p = 0.011$) was lower in Group 2 compared to Group 1. Specific details are presented in Table 4.

No serious drug-related adverse reactions occurred in any of the patients after treatment with treprostinil.

Discussion

In pediatric patients post-TCPC surgery, the absence of a subpulmonary ventricle makes minimizing pulmonary artery pressure a crucial factor determining pulmonary circulation. Even mild increases in pulmonary artery pressure can decrease cardiac output and increase central venous pressure, which is unfavorable for Fontan circulation. Therefore, the application of targeted PAH medications to reduce pulmonary artery pressure becomes pivotal for the success of the surgery [12].

Table 1 Demographic characteristics of the two patient groups

Variable	Group 1 (n = 35)	Group 2 (n = 16)	p-value
Age (years)	4.6(3.6, 7)	5.8(4.2,12)	0.127
Gender (n, %)			
Male	17(49)	10(62)	0.355
Female	18(51)	6(38)	
Weight (kg)	16(14, 23)	19(15, 33)	0.242
Peripheral oxygen saturation (%)	79 ± 6	79 ± 7	0.98
Hemoglobin concentration (g/L)	175 ± 26	172 ± 26	0.757
Heterotaxy syndrome (n, %)	11(31)	2(13)	0.274
mPAP(mmHg)	17 ± 2	17 ± 3	0.289

Table 2 Surgical data of the two patient groups

	Group 1 (n = 35)	Group 2 (n = 16)	p-value
TCPC procedure (n, %) Side-to-side tunnel Extra-cardiac conduit	5(14) 30(86)	2(13) 14(87)	1.0
Concomitant procedures (n, %)	18(51)	7(44)	0.611
TCPC fenestration (n, %)	28(80)	12(75)	0.971
Cardiopulmonary bypass time (minutes)	166 ± 52	146 ± 47	0.181
Aortic cross-clamp (n, %)	23(66)	8(50)	0.286

Table 3 Hemodynamic changes of two groups of patients

	Baseline	6 h	12 h	18 h	24 h	p-value
mPAP (mmHg)	17 ± 3	16 ± 3	16 ± 2	16 ± 2	15 ± 2	< 0.001
Group1	17 ± 2	15 ± 2	15 ± 1	14 ± 1	14 ± 2	< 0.001
Group 2						0.18
Inter-group						
VIS	10 (7,15)	9 (7, 15)	10 (6, 14)	10 (6, 13)	9 (6, 13)	0.114
Group1	9 (5, 15)	7 (3, 14)	7 (3, 15)	8 (3, 14)	8 (3, 14)	0.247
Group 2						0.473
Inter-group						

VIS vasoactive inotropic score

Table 4 Postoperative recovery indicators for two patient groups

	Group 1 (n = 35)	Group 2 (n = 16)	p-value
Mechanical ventilation duration (hours)	69 (23, 189)	19 (11, 25)	0.001
ICU length of stay (days)	16 (9, 26)	8(6, 12)	0.006
Postoperative length of stay (days)	39 (29, 58)	27(17, 55)	0.032
Duration of chest tube drainage (days)	34(20, 47)	23(14, 36)	0.113
Chest tube drainage volume (ml/kg)	261(163, 484)	152(94, 316)	0.054
Thromboembolic events (n, %)	9(26)	0(0)	0.043
Supraventricular arrhythmias (n, %)	14(40)	3(19)	0.241
Renal replacement therapy (n, %)	11(31)	0(0)	0.011
Neurological complications (n, %)	5(14)	0(0)	0.167
Multiple endotracheal intubations	6(17)	1(6)	0.542
Tracheostomy	5(14)	0(0)	0.167
Mortality	0(0)	0(0)	NA

Currently, commonly used targeted medications include nitric oxide pathway agents, endothelin pathway agents, and prostacyclin pathway agents [13]. In China, apart from inhaled nitric oxide and intravenous/subcutaneous treprostinil, all other medications are administered orally. However, in the early post-TCPC period, gastrointestinal function has not yet recovered, and the efficacy of oral medications depends on gastrointestinal absorption, which may delay achieving stable therapeutic effects. Although inhaled nitric oxide has proven efficacy, its administration depends on ventilator support and is only suitable for use during mechanical ventilation. Therefore, the use of intravenous treprostinil as a bridging therapy between inhaled and oral targeted medications, achieving seamless management of targeted drug therapy post-TCPC surgery, is theoretically feasible and represents a promising treatment strategy.

The application of treprostinil in the treatment of single-ventricle with concomitant PAH patients is currently supported by limited research in both quantity and level of evidence. Chen X and colleagues reported on a self-controlled study of 8 patients (5 post-Glenn procedure, 3 post-TCPC procedure) who received early postoperative intravenous treprostinil. Following an average treatment dosage of 55 ng/(kg·min) of treprostinil, significant improvements were observed in mPAP, pulmonary/systemic pressure ratio, and arterial oxygen partial pressure/inhaled oxygen concentration [9]. Sullivan RT and colleagues reported a self-controlled study of 17 patients who received long-term subcutaneous treprostinil infusion at 20–30 ng/ (kg·min) to improve hemodynamic parameters in high-risk single-ventricle patients and facilitate surgical opportunities. The study found that treprostinil not only reduced pulmonary vascular resistance, but also demonstrated that in most patients, pulmonary vascular resistance did not rebound after discontinuation. Regarding the pursuit of surgical opportunities, among 11 patients undergoing stage I (palliative shunt) procedures, 9 (82%) gained the opportunity for Glenn procedure, while among 6 patients post-Glenn procedure, 3 (50%) gained the opportunity for TCPC procedure [10].

Since 2015, our center has been employing treprostinil to treat high-risk TCPC postoperative patients with concomitant PAH. Initially, due to insufficient experience and concerns regarding the passive pulmonary

circulation following TCPC, compounded by inadequate effective circulating blood volume in the early postoperative period [14], the dosage escalation of treprostinil was cautious, with a slow titration rate and maintenance dosage selection based on the drug's effectiveness. Subsequently, no further dose escalation was pursued. With increasing experience, a standardized approach was initiated in 2021, with expedited dosage escalation and maintenance dose selection based on the maximum tolerated dose by patients. The primary aim of this study is to compare these two distinct dosing strategies and their impact on improving patients' hemodynamic parameters and postoperative recovery indicators.

Regarding the hemodynamic improvement, observations made 24 h after medication administration revealed that treprostinil effectively and steadily reduced pulmonary arterial pressure in TCPC postoperative patients in both Group 1 and Group 2, suggesting that targeted pharmacotherapy remains effective in reducing pulmonary arterial pressure in single-ventricle patients with concomitant PAH. Although patients in Group 2 exhibited a greater reduction in pulmonary arterial pressure compared to Group 1, no statistically significant difference was found. In terms of circulatory stability, given the varying target blood pressures for children of different ages, this study did not directly compare absolute blood pressure values. Instead, it analyzed the change in vasoactive inotropic score required to maintain satisfactory blood pressure, thereby assessing the effectiveness and safety of drug therapy. In both Group 1 and Group 2 patients, no statistically significant difference was observed in the change in vasopressor score following treprostinil administration, indicating minimal impact on systemic blood pressure under the maintenance dosage used in this study, thus suggesting a higher level of safety.

In terms of improving postoperative recovery indicators, patients in Group 2 exhibited significant advantages over those in Group 1 in mechanical ventilation time, ICU length of stay, postoperative hospital stay, incidence of thromboembolic events, and need for renal replacement therapy. Regarding the underlying reasons, although there was no statistically significant difference in the reduction of pulmonary arterial pressure between the two groups following treprostinil treatment, treprostinil's pharmacological effects extend beyond reducing pulmonary vascular resistance. It includes reducing systemic ventricular afterload, inhibiting platelet aggregation, and suppressing smooth muscle cell proliferation [15]. It is plausible that the higher dosage of treprostinil in Group 2 exerted its comprehensive pharmacological effects, thereby improving patients' surgical outcomes. Furthermore, the superior postoperative recovery indicators in Group 2 patients further underscore the safety and efficacy of standardized treprostinil treatment.

In addition to treprostinil, all patients enrolled in this study also received other targeted drugs, such as inhaled nitric oxide and oral bosentan/sildenafil, which also played an important role in improving postoperative recovery in high-risk TCPC patients. The high-risk patients included in this study were seriously ill, but all of them survived in the postoperative period, which may be due to targeted drug sequential therapy. The purpose of treprostinil in our study was to bridge the window period when inhaled nitric oxide cannot be continued after tracheal extubation and oral drugs cannot be effective before gastrointestinal function recovery after the TCPC procedure. In this condition, the difference between the two groups of patients existed in the treprostinil administration regimen, which may have led to an improvement in recovery in the standardized treatment group.

Nevertheless, this study has several limitations. Firstly, the small sample size may have led to a lack of statistical power to detect clinically significant differences. Future studies should aim at expand the sample size or conduct multicenter research to address this limitation. Secondly, the duration of mechanical ventilation, intensive care unit stay, and postoperative length of stay may be influenced by multiple factors. It is difficult to draw a firm conclusion from the retrospective nature of the study, the evidence level remains suboptimal. Future research should consider conducting randomized controlled trials or matched cohort studies to strengthen the evidence base. Thirdly, since our center's surgeons do not routinely insert atrial pressure monitoring catheters, the hemodynamic parameters in this study were not comprehensive. Future studies could consider utilizing monitoring systems such as PICCO to refine hemodynamic parameters.

Conclusion

In patients with single ventricle and concomitant PAH undergoing TCPC surgery, the use of treprostinil can reduce pulmonary arterial pressure without serious adverse reactions. Standardized treprostinil administration (achieving the maintenance dosage within 24 h postoperatively, i.e., the maximum tolerated dose) may improve the postoperative recovery which should be proven by randomized controlled trials or matched cohort studies in the future.

Author contributions

Xiaofeng Wang and Shilin Wang contributed to the article writing, data collection, and statistical analysis. Ruihuan Shen and Zhongyuan Lu drafted and critically reviewed the manuscript. Xu Wang contributed to the study design and the review of the final article. All authors contributed to the manuscript and approved the submitted version.

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Availability of data and material
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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References

1. Becker K, Uebing A, Hansen JH. Pulmonary vascular disease in Fontan circulation—is there a rationale for pulmonary vasodilator therapies? Cardiovasc Diagn Ther. 2021;11(4):1111–21.
2. Al-Shawk M, Banjoko A, Axiaq A, Amin K, Harky A. Perioperative and long-term management of Fontan patients. Cardiol Young. 2021;31(5):775–85.
3. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.
4. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42(6):563–645.
5. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, et al. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation. 2011;123:1185–93.
6. Rhodes J, Ubeda-Tikkanen A, Clair M, Fernandes SM, Graham DA, Milliren CE, et al. Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. Int J Cardiol. 2013;168:2435–40.
7. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E, et al. Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (treatment with endothelin receptor antagonist in fontan patients, a randomized, placebo-controlled, double-blind study measuring peak oxygen consumption) study. Circulation. 2014;130:2021–30.
8. Constantine A, Dimopoulos K, Jenkins P, Tulloh RMR, Condliffe R, Jansen K, et al. Use of pulmonary arterial hypertension therapies in patients with a fontan circulation: current practice across the United Kingdom. J Am Heart Assoc. 2022;11(1): e023035.
9. Ablonczy L, Tordas D, Kis E, Szatmári A. Use of subcutaneous Treprostinil in pediatric pulmonary arterial hypertension-Bridge-to-transplant or long-term treatment? Pediatr Transplant. 2018;22:2.
10. Chen X, Cai XM, Zhang MJ, Xu JH, Li H, Xu ZM. Pharmacokinetics of Treprostinil in children with functional single-ventricle pulmonary arterial hypertension: a randomized controlled trial. Ann Transl Med. 2021;9(14):1163.
11. Sullivan RT, Handler SS, Feinstein JA, Ogawa M, Liu E, Ma M, et al. Subcutaneous treprostinil improves surgical candidacy for next stage palliation in single ventricle patients with high-risk hemodynamics. Semin Thorac Cardiovasc Surg. 2022;S1043–0679(22):00191–5.
12. Jeremiasen I, Tran-Lundmark K, Idris N, Tran PK, Moledina S. Pulmonary vasodilator therapy in children with single ventricle physiology: effects on saturation and pulmonary arterial pressure. Pediatr Cardiol. 2020;41(8):1651–9.
13. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension: a review. JAMA. 2022;327(14):1379–91.
14. Siddall E, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int. 2017;92(1):37–46.
15. Skoro-Sajer N, Lang I, Naeije R. Treprostinil for pulmonary hypertension. Vasc Health Risk Manag. 2008;4(3):507–13.

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