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Efficacy of inhaled iloprost in children with pulmonary hypertension after pediatric cardiac surgery: a case series

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Abstract

Background The postoperative phase of cardiac surgery in pediatric patients with congenital heart disease often involves the management of pulmonary hypertension, which can significantly affect recovery and long-term prognosis. Inhaled iloprost is a potent acute pulmonary vasodilator with a rapid onset of action and has been shown to be effective and safe in patients with pulmonary arterial hypertension, improving clinical parameters by lowering pulmonary artery pressure. In our study, we will share the results of patients with pulmonary hypertension after pediatric cardiac surgery in whom we used inhaled iloprost.

Results A total of 9 patients who received inhaled iloprost between 2020 and 2023 were included in the retrospective study. The age of the patients ranged between 10 days and 11 months, with a mean of 207.77 days (6.92 months) ± 105.78 days (3.52 months). Five patients were male (55.55%), and four were female (44.45%). Three of the patients had trisomy 21 (33.3%) genetic mutations.

Conclusions The limited number of case series in the literature support the potential of inhaliloprost as an effective and safe therapeutic option for the treatment of pulmonary hypertension in the pediatric population after congenital heart surgery. The findings of this study support the literature and suggest that inhaliloprost is effective. Due to the limited number of patients, further research is needed to determine the safety and efficacy of these drugs, especially to determine the dose, route, and duration of administration in intubated patients.

Keywords Inhaler iloprost, Pulmonary hypertension, Iloprost, Nebul, Pediatric cardiac surgery

Background

Pulmonary hypertension and associated right heart failure are common in congenital heart disease patients. It is a cause of serious mortality and morbidity, especially in the early postrepair period. The development of pulmonary hypertension after pediatric cardiac surgery is a critical concern because of its potential adverse effects on postoperative patient outcomes. The postoperative period of cardiac surgery in pediatric patients with congenital heart disease often involves the management of pulmonary hypertension, which can significantly impact recovery and long-term prognosis. In addition, the influence of factors such as cardiopulmonary bypass,

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hypothermia, circulatory arrest, and inotropes on the development of increased vasoconstriction via different mechanisms has been highlighted as important contributors to the development of pulmonary hypertension after pediatric cardiac surgery [1]. The management of pulmonary hypertension after pediatric cardiac surgery is a multifaceted challenge that requires an approach encompassing different interventions and careful evaluation of the factors contributing to its development [2].

Inhaliloprost is a well-established drug for the treatment of pulmonary arterial hypertension (PAH), a serious and potentially fatal disease of the pulmonary arteries [3]. Inhaliloprost has been shown to be a potent pulmonary vasodilator with more pronounced short-term hemodynamic effects than inhaled nitric oxide. In addition, in the context of pediatric patients undergoing congenital heart surgery, inhaled iloprost was found to significantly improve hemodynamics in a dose-dependent manner and prevent reactive pulmonary hypertension and pulmonary hypertensive crises [4]. In summary, inhaled iloprost is a potent acute pulmonary vasodilator with a rapid onset of action and has been shown to be effective and safe in improving clinical parameters by regulating pulmonary arterial pressure in patients with primary pulmonary arterial hypertension [5].

Although inhaled iloprost has been proven to improve symptoms, pulmonary hemodynamics, and prognosis in patients with idiopathic (primary) pulmonary arterial hypertension, evidence for the perioperative use of iloprost in cardiac surgery is limited mainly to case reports and observational studies. In our study, we will share the results of patients with pulmonary hypertension after pediatric cardiac surgery in whom we used inhaled iloprost.

Methods

This retrospective study included 9 patients who received inhaled iloprost between May 2021 and June 2023. After the first dose of inhaleriloprost, a 2-year-old VSD patient who developed a side effect of redness reaction on the skin was discontinued, and sildenafil was started; this patient was not included in the study. The medical records of the patients were obtained from the hospital information system and archive search.

Patients underwent frequent echocardiograms pre- and postoperatively, including after iloprost inhalation. Tricuspid regurgitation was used to estimate pulmonary artery pressure. Pulmonary hypertension was defined as a mean PAP greater than 25 mmHg in the first postoperative period. The eligibility criteria and implementation of the protocol were based on the joint decision of the pediatric cardiologist, pediatric cardiovascular surgeon, and intensive care physician, and echocardiography revealed a right-to-left shunt or bidirectional shunt in patients. Standard postoperative care analgesia and sedation (fentanyl 2–25 mcg/kg/h; midazolam 0.1–1 mg/kg/h) were administered. Milrinone infusion was started to increase end diastolic compliance to relieve afterload, and oral sildenafil was administered as needed after 3 days of inhaled iloprost therapy.

Surgical treatment was standardized during this study. Intracardiac repair was performed through median sternotomy with standard cardiopulmonary bypass using bicaval cannulation, moderate hypothermia at 28–32 C, and antegraddelnido cardioplegia. Antegrade cerebral perfusion was performed in patients who underwent arch reconstruction. After all, patients were weaned from cardiopulmonary bypass and warmed, and blood pressure in the pulmonary artery and aorta was measured via invasive pressure lines connected to the hemodynamic monitoring system.

Postoperative invasive systemic pressure was correlated with pulmonary artery pressure during daily echocardiography. Intensive care, intubation, and hospitalization times were extracted from the medical records.

The postoperative ventilation circuit was connected to a Servo 900C anesthesia ventilator (Siemens Erlangen, Germany). Iloprost (20 µg/2 mL, Ventavis, Bayer, Leverkusen, Germany) was administered by integrating a nebulizer into the ventilator circuit near the humidifier at a weight-appropriate dose every 2 h according to the protocol used for inhaled iloprost therapy in postoperative patients with pulmonary hypertension (Table 1) [6].

Arterial blood gases were checked, and respiratory parameters were recorded at regular intervals (every 2 h). The ratio of partial arterial oxygen pressure (PaO2) to the fraction of inspired oxygen (FiO2) was calculated at regular intervals.

Weaning from mechanical ventilation was planned to be performed as soon as possible after surgery because it is known that if it takes too long to stabilize the patient, the patient will be at risk of developing secondary infections and may die from these infections. Although PHT

Table 1 Inhaled iloprost dosing

Weight (kg)	Starting dose (µg)	Frequency	High dose (µg)
< 5	1.25	Every 2 h	2,5
5–10	2.5	Every 2 h	5
10–15	3.75	Every 2 h	7,5
15–20	5	Every 2 h	10
20–25	6.25	Every 2 h	12,5
25–50	7.5	Every 2 h	15
> 50	10	Every 2 h	20

patients were previously intubated under sedation in our clinic for the first 24–48 h and hemodynamic stabilization was maintained, this practice has been abandoned, and we now make decisions according to the patient's clinic. Extubated patients were not included in the study. Intubated patients receiving intubated inhaled iloprost were included.

The study was conducted retrospectively with the permission of the hospital administration and in accordance with the Declaration of Helsinki and ethical rules.

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, UT, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used to evaluate the study data.

Results

The study included 9 patients. The ages of the patients ranged between 10 days and 11 months, with a mean age of 207.77 (6.92 months) ± 105.78 days (3.52 months). Five patients were male (55.55%), and four were female (44.45%). Three of the patients had trisomy 21 (33.3%) genetic mutations. Among the 9 postoperative patients, 3 patients (33.33%) underwent AVSD repair, 2 patients (22.22%) underwent VSD closure, 1 patient (11.11%) underwent supracardiac TAPVD repair, 1 patient (11.11%) underwent truncus areriosus repair, 1 patient (11.11%) underwent LVOTO removal + aortic arch reconstruction, and 1 patient (11.11%) underwent extensive aortic arch reconstruction. The cross-clamp time ranged between 34 and 98 min, with a mean of 62.77 ± 23.47 min. The total cardiopulmonary bypass time ranged between 59 and 130 min, with a mean of 92.44 ± 23.37 min.

The mean pulmonary artery pressure (PAB) determined via echocardiography in the preoperative period ranged between 40 and 85 mmHG, with a mean value of 61.66 ± 13.54. The mean pulmonary artery pressure (PAP) before postoperative treatment ranged between 50 and 100 mmHG, with a mean value of 75 ± 15.09 mmHg. After postoperative treatment, the mean pulmonary artery pressure (PAP) ranged between 30 and 65 mmHG, with a mean value of 47.77 ± 10.57 mmHg. Preoperative noninvasively measured blood pressure ranged from 62 to 94 mmHG, with a mean value of 72.22 ± 9.39 mmHg. Postoperative invasive systolic blood pressure ranged from 74 to 102 mmHG, with a mean value of 81.55 ± 9.58 mmHg. Postoperative invasive systolic blood pressure ranged between 52 and 110 mmHG, with a mean of 80.77 ± 17.97 mmHg after treatment (Fig. 1).

The mean MAP (mean airway pressure) of the patients before treatment ranged between 14 and 29 cmH2O, with a mean of 21.88 ± 4.83 cmH2O. The mean posttreatment MAP (mean airway pressure) ranged between 15 and 25 cmH2O, with a mean of 21.11 ± 3.29 cmH2O. The pretreatment FiO2 (%) of the patients ranged between 45 and 85 cmH2O, with a mean of 63.33 ± 14.14 cmH2O. The posttreatment FiO2 (%) of the patients ranged between 30 and 60 cmH2O, and the mean value was 42.77 ± 8.7 cmH2O. The pretreatment partial oxygen tension of the patients ranged between 25 and 84 mmHg, with a mean of 54.33 ± 20.75 mmHg. The posttreatment partial oxygen tension ranged between 38 and 88 mmHg, with a mean of 56.44 ± 16.22 mmHg. The oxygenation index ranged between 9 and 65.5, with a mean of 25.72 ± 15 before treatment, and ranged between 11.42

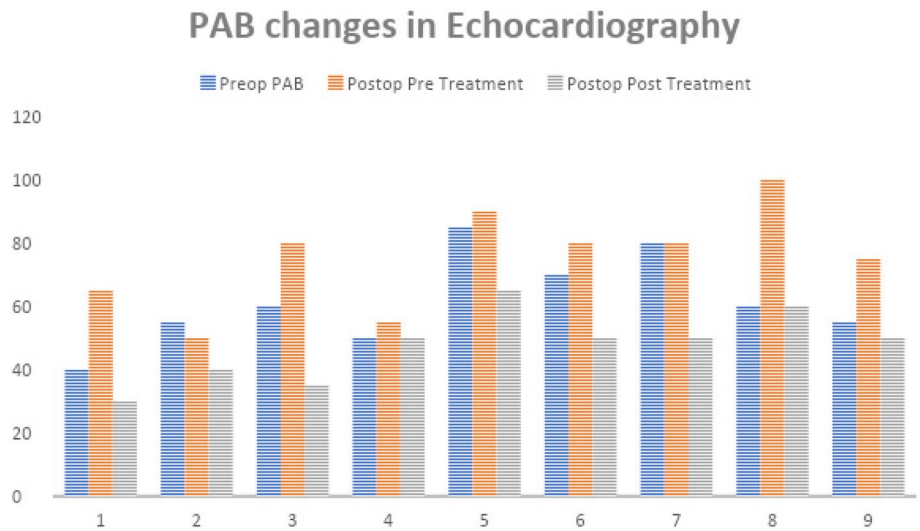

Fig. 1 Graph showing the change in mean pulmonary artery pressure before and after preoperative postoperative treatment

and 22.22, with a mean of 16.57 ± 15 3.85 after treatment (Fig. 2).

The incubation duration ranged between 4 and 28 days, with a mean of 10.88 ± 7.42 days. The duration of intensive care unit stay varied between 8 and 38 days, with a mean of 18.22 ± 9.82 days. The total hospital stay ranged between 12 and 49 days, with a mean of 26.55 ± 11.11 days.

Discussion

When given as an inhaled agent, iloprost, a prostaglandin I2 (PGI2) analog and vasodilator, induces selective pulmonary vasodilation. This property optimizes drug delivery to ventilated areas of the lung while minimizing the risk of systemic vasodilation. This aerosolized delivery method also reduces the potential risks associated with intravenous or subcutaneous prostacyclin administration. It should be kept in mind that inhaleriloprost administration may be advantageous when alternative therapeutic options for the management of pediatric pulmonary hypertension in the intensive care setting are considered [6].

The only approved treatment for persistent pulmonary hypertension in newborns is inhaled nitric oxide, which is provided by a private company in Turkey. Alternative therapies should be considered because they are sometimes difficult to administer. In the literature, inhaliloprost is recommended alone or as adjunctive therapy. It is easily available and has favorable clinical effects. Yıldırım reported favorable results in the treatment of primary PHT in a study of 6 newborns [7]. We shared the results of 9 patients in whom we used inhaleriloprost due to PHT after congenital cardiac surgery and wanted to share our experience using inhaleriloprost and its positive results in the early period, although the number of cases was small.

Further investigation and standardization of dosing regimens are warranted to optimize the use of inhaliloprost in the pediatric population. There are no specific guidelines for inhaled iloprost in terms of dosage or timing. In humans, the biological half-life is 20–30 min [6–8]. In our study, the starting dose was determined according to the patient's weight (Table 1). We still face the same problem in these small case studies, as no dose–response or dose efficacy was reported, and multiple different dosages were used, which does not allow recommendations for dose administration in this population. Moreover, these patients were on mechanical ventilation and ventilated with different ventilation modes, which increases the difficulty of assessing the dose given to the patient [3, 9]. In our study, determining the dose and mode of administration, especially in intubated patients, was challenging for the team due to limitations in the available literature.

A prospective randomized pilot study by Loukanov et al. showed that inhaleriloprost was as effective as iNO in the management of postoperative PH experienced by patients with congenital heart disease, with comparable PAP measurements and frequencies of PH crises [8, 10]. In our case series, we observed a decrease in pulmonary pressure in 8 out of 9 patients. In our study, the mean pulmonary artery pressure decreased from 75 ± 15.09 mmHg on echocardiographic examination before treatment to 47.77 ± 10.57 mmHg after treatment in the postoperative period.

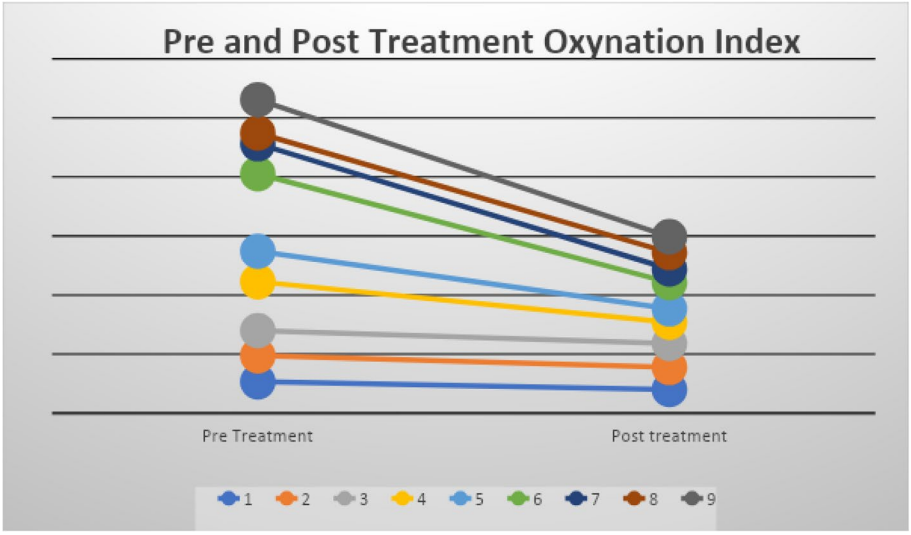

Fig. 2 Changes in the oxynation index after inhaleriloprost treatment

The available literature suggests that a transient significant decrease in pulmonary hemodynamics occurs during short- to medium-term inhaliloprost treatment; this is probably related to endothelial cell remodeling and suggests that a new oral or intravenous PAH-specific agent may need to be added to treatment in the long term to prevent progressive proliferation in the pulmonary circulation [11]. In our study, we started oral sildenafil after inhaled treatment. We believe that oral sildenafil is more beneficial in the long term because of its ease of use and proven effects.

Inhaliloprost treatment causes some common adverse reactions to prostanoids, such as headache and cough, in approximately 30% of patients and rarely leads to hypotension in patients who use it for more than 3–12 months [12]. It was not possible to evaluate cough and headache, which are common in patients after inhalation of iloprost, because we used these measures in intubated patients. Although we did not encounter such side effects in our case series, one of our patients developed a skin reaction, inhaleriloprost treatment was stopped, and he was followed up with oral sildenafil.

Inhaled iloprost is a more stable prostacyclin with a longer elimination time than inhaled nitric oxide and an effective pharmacological half-life in the pulmonary vasculature of 21–25 min, which also offers the advantage of intermittent dosing. Intermittent administration of pulmonary vasodilator therapy instead of the continuous administration of inhaled NO (or inhaled epoprostenol) has been reported to be an unexpected advantage in the postoperative period because it is less burdensome for patient care and makes transportation for emergency imaging or procedures safer and easier [6]. Furthermore, although our study did not include a cost-effectiveness analysis, it is known to be less expensive and more readily available than its alternative, inhaled nitric oxide, for the treatment of PHT in our country.

The systemic inflammatory response induced by cardiopulmonary bypass manifests as increased pulmonary capillary permeability, decreased pulmonocompensation, and increased PVR, which compromises right ventricular contractility and may ultimately lead to acute right ventricular decompensation. Intravenous administration of iloprost has previously been shown to improve ventricular dysfunction and facilitate weaning from CPB. However, the incidence of systemic hypotension due to intravenous administration is high, and patients often require inotropic support. [13]. In our study, the mean systemic pressure was 81.55 ± 9.58 mmHg before iloprost inhalation and 80.77 ± 17.97 mmHg after treatment. Although the number of patients did not reach statistical significance, the mean difference between pre- and post-treatment systemic blood pressure values was very low.

Sildenafil has been shown to inhibit PHT by reducing basal pulmonary artery pressure (PAP) and pulmonary vascular resistance, potentially through effects on cyclic guanosine monophosphate (cGMP) and nitric oxide (NO) pathways. Furthermore, the vasodilatory effects of sildenafil have been shown to be selective to the pulmonary circulation, making it a potent pulmonary vasodilator in children with congenital heart disease and PHT [14, 15]. Sildenafil has also been found to inhibit β-adrenergic-stimulated cardiac contractility in humans, with a significant interaction reported in the presence of catecholamine stimulation [16]. Iloprost, a synthetic analog of a type of prostaglandin known as prostaglandin I2 (PGI2), has been shown to inhibit the Ras/MEK/ERK pathway, thereby preventing the fibrotic response to TGFβ2. Furthermore, iloprost was found to regulate thrombomodulin expression in human vascular smooth muscle cells, indicating its role in modulating gene expression and cell movement. It has also been shown to inhibit inositol-1,4,5-triphosphate-mediated calcium mobilization through cAMP through secondary inhibition of L-type calcium entry channels, providing insights into its effect on calcium signaling in vascular smooth muscle cells [16].

In addition, perioperative inhaliloprost therapy has demonstrated the benefit of cardiac functional improvement and early cessation of postoperative supportive care in the treatment of congenital heart disease with pulmonary arterial hypertension, shortening the need for intensive care [5]. Furthermore, case reports have highlighted the successful use of inhaled iloprost to stabilize infants with complex congenital heart defects and severe pulmonary arterial hypertension [17].

The use of nebulizers, especially in the context of the administration of drugs such as iloprost, may increase the risk of infection transmission. Nebulizers have been identified as potential sources of aerosol production and dispersion that may contribute to the transmission of infectious agents, including bacteria and viruses. This is of particular concern in the context of respiratory infections and conditions because the use of nebulizers has been associated with an increased risk of infection transmission, particularly in healthcare settings. Furthermore, the cleaning and maintenance of nebulizers play crucial roles in reducing the risk of infection transmission. Proper cleaning and disinfection of nebulizers is crucial for preventing contamination and reducing the potential for the spread of infection [18, 19]. We paid attention to infection precautions to reduce transmission as much as possible and informed our assistant staff about this issue.

Treatment of pulmonary hypertension in pediatric patients is a complex and challenging task. Studies have investigated various drugs, including inhaled iloprost,

sildenafil, and inhaled nitric oxide, and have shown potential benefits in improving pulmonary hemodynamics and outcomes in this specific patient population [14]. This retrospective study included a limited number of patients treated with inhaleriloprost; further studies are needed to define the role of inhaleriloprost in the treatment of pulmonary hypertension.

Conclusions

Limited case series in the literature support the potential of inhaled iloprost as an effective and safe therapeutic option for the treatment of pulmonary hypertension in the pediatric population after congenital heart surgery. The findings of this study support the literature and suggest that inhaled iloprost is effective. Due to the limited number of patients, further research is needed to determine the safety and efficacy of these drugs and to determine the dose and route of administration, especially in intubated patients.

Abbreviations

PAH	Pulmonary arterial hypertension (PAH)
PAP	Pulmonary artery pressure
cGMP	Cyclic guanosine monophosphate (cGMP)
NO	Nitric oxide (NO)
PGI2	Prostaglandin I2
CPB	Cardiopulmonary bypass
MAP	Mean airway pressure
PaO2	Partial arterial oxygen pressure
FiO2	Fraction of inspired oxygen

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Authors' contributions

Study design by EA, KAK, and SB; data collection by EA, MAY, FY, SH, and ZGKÖ; writing by EA, FY, and KAK; supervising by ARK and SB. Final approval by all authors. All authors have read and approved the manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the hospital management. The study is retrospective, and consent to participate was waived by the IRB. The committee's reference number is not applicable. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Specific research consent was not obtained and waived. Before surgery, written informed consent to publish this information was obtained from the study participants' next of kin and/or parent/legal guardian.

Competing interests

The authors declare that they have no competing interests.

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