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RESEARCH ARTICLE

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Inhaled iloprost is an effective alternative therapy for persistent pulmonary hypertension in newborns

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is one of the diseases of the neonate with severe potential morbidity and mortality. Inhaled iloprost, a stable prostacyclin analog, has been suggested as an alternative treatment for inhaled nitric oxide (iNO). However, more data on neonates' dosing, setting, and effectiveness still needs to be solved. This study suggests using inhaled iloprost as rescue therapy for PPHN based on our experience. This was a retrospective study. The data from medical records of six newborns diagnosed with PPHN and had received inhaled iloprost from December 2019 to April 2022 were collected. Demographic and clinical features, dosing regimen, changes in oxygenation index, echocardiographic findings, and mortality were evaluated. The inhalation dose was 2–4 mcg/dose, and 3–48 inhalations per day were applied over 2–7 days. Inhaled iloprost was effective in all patients. No side effects were attributable to inhaled iloprost, and no mortality was recorded. Our experience suggests that inhaled iloprost can be used as a first-line therapy in newborn infants with PPHN when iNO is unavailable. However, there are large fluctuations in the oxygenation index due to the setting.

KEYWORDS
inhaled iloprost, persistent pulmonary hypertension of the newborn, prostacyclin

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) results from a failure of the newborn's normal circulatory transition, characterized by marked hypoxemia secondary to right-to-left extrapulmonary shunting of deoxygenated blood. Generally, it is a disease of the term or near-term neonates. The incidence of PPHN ranges from 0.4 to 6.8 per 1000 live births,[1] with an associated mortality of 4– 60%.[2,3] Also, significant long-term morbidities of up to 25% are reported.[2]

The pathophysiological process of PPHN may involve acute pulmonary vasoconstriction, pulmonary vascular remodeling, pulmonary vascular hypoplasia, or pulmonary intravascular obstruction.[4–6]

Echocardiography is necessary to rule out cyanotic congenital heart disease.[7] A specific pulmonary artery pressure is defined for adult primary pulmonary hypertension, not PPHN. Right-to-left shunt without congenital heart disease is enough for diagnosing PPHN, regardless of the pulmonary arterial pressure.[5]

TABLE 1 Demographic and clinical features of neonates with persistent pulmonary hypertension.

Patient no	1	2	3	4	5	6
Birthweight (g)	3380	3905	2250	2320	3215	3400
Delivery method	C/S	NVD	C/S	C/S	C/S	NVD
Gender	Male	Female	Female	Male	Male	Female
Gestational age	35 w 6 d	38 w	34 w	36 w 2 d	38 w	39 w
Diagnose	Infant of a diabetic mother, cerebral ventriculomegaly, resuscitation, and intubation in the delivery room	Convulsion, Chronic intrauterine hypoxia? No pregnancy follow-up, intubated at postnatal 9 h	Infant of a mother with SARS-CoV-2 pneumonia,[a] resuscitation, and intubation in the delivery room, acute renal failure, grade 4 IVH	Infant of a mother with gestational hypertension, resuscitation and intubation in the delivery room	Infant of a diabetic mother, birth trauma, resuscitation, and intubation in the delivery room, convulsions	Perinatal asphyxia, meconium aspiration syndrome, resuscitation and intubation in the delivery room
Oxygenation index before iloprost treatment	9	18	21	23	9	15
Age at referral (h)	38	31	51	9	44	2.5
Pulmonary artery pressure (basal and at the end of therapy) (mm/Hg)	45/25	60/NA	45/20	60/45	55/18	35/25
Iloprost treatment duration (h)	156	61	205	77	152	52
Maximal dose (mcg/day)	14	12	70	48	192	36
Cumulative dose (mcg)	62	66	230	92	510	64
Inotrope	−	+	+	+	+	+
Surfactant (100 mg/kg)	2 doses	(−) (considered CCHD at first)	1 dose	1 dose	2 doses	2 doses
Response to surfactant	FiO_2 remained >40% after two doses	−	No use, FiO_2 remained 100%	No use, FiO_2 remained 100%	FiO_2 remained >40% after two doses	FiO_2 remained >40% after two doses

TABLE 1 (Continued)

Patient no	1	2	3	4	5	6
Chest X-ray	Hyperaeration	Hyperaeration	Patchy infiltrates in the left lung, hyperaeration in the right lung	Hyperaeration	Normal	Patchy infiltrates
Sedative	+	+	+	+	+	+
Hospitalization (d)	19	25	27	10	14	14

Abbreviations: CCHD, congenital cyanotic heart disease; C/S, cesarean section; d, day; g, gram; h, hour; IVH, intraventricular hemorrhage; MAS, meconium aspiration syndrome; mcg, microgram; NVD, normal vaginal delivery; OI, oxygenation index; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; w, week.

[a]The baby was SARS-CoV-2 negative.

Inhaled nitric oxide (iNO) is the only approved pulmonary vasodilator for treating PPHN. Nevertheless, it does not improve survival, and ~40% of neonates fail to respond.[8] It is still unclear whether iNO is safer and more effective than other vasodilators delivered by inhalation, such as inhaled prostacyclin.[8] Therefore, investigation of the efficacy and safety of other potential therapeutic agents, such as pulmonary vasodilators like prostanoids, phosphodiesterase inhibitors like sildenafil and milrinone, and endothelin antagonists like bosentan is ongoing.[9–12]

Acquired neonatal diseases like meconium aspiration syndrome, asphyxia, sepsis, transient tachypnea of the newborn, and respiratory distress syndrome may cause PPHN as well as congenital diseases like diaphragmatic hernia, alveolar capillary dysplasia, surfactant protein defects and cardiac defects.[13] Increased pulmonary vascular resistance is the final result of the above.[14] Prostacyclin, a naturally occurring prostaglandin, is a potent vasodilator with antithrombotic, antiproliferative, and anti-inflammatory effects.[15] The convenience for the prostacyclin analogs to treat PPHN is evident.[16,17] Iloprost is an analog of prostacyclin with more excellent chemical stability, making it practical for treatment purposes.[18] Prostacylin has been used and studied over time for PPHN.[19] Several reports have addressed inhaled iloprost treatment for pulmonary hypertension in the newborn literature,[19–35] all of which emphasize the need for further research. So, to contribute to the literature, six patients with PPHN treated with inhaled iloprost because of lack of accessibility to iNO are presented in detail in this article, and potential obstacles for iloprost inhalation use are discussed.

MATERIALS AND METHODS

We retrospectively analyzed the records of 6 patients with PPHN treated with inhaled iloprost at neonatal intensive care at the University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, between December 2019 and April 2022. Demographic and clinical features of neonates with persistent pulmonary hypertension are presented (Table 1). The eligibility criteria for inhaled iloprost treatment in persistent pulmonary hypertension on clinical basis of our unit are shown (Source file 1). Inhaled iloprost (20 μg/2 mL, Ventavis, Bayer, Leverkusen, Germany) was administered at a dose of 2−4 mcg (microgram) every 1/2−8 h according to the protocol used for

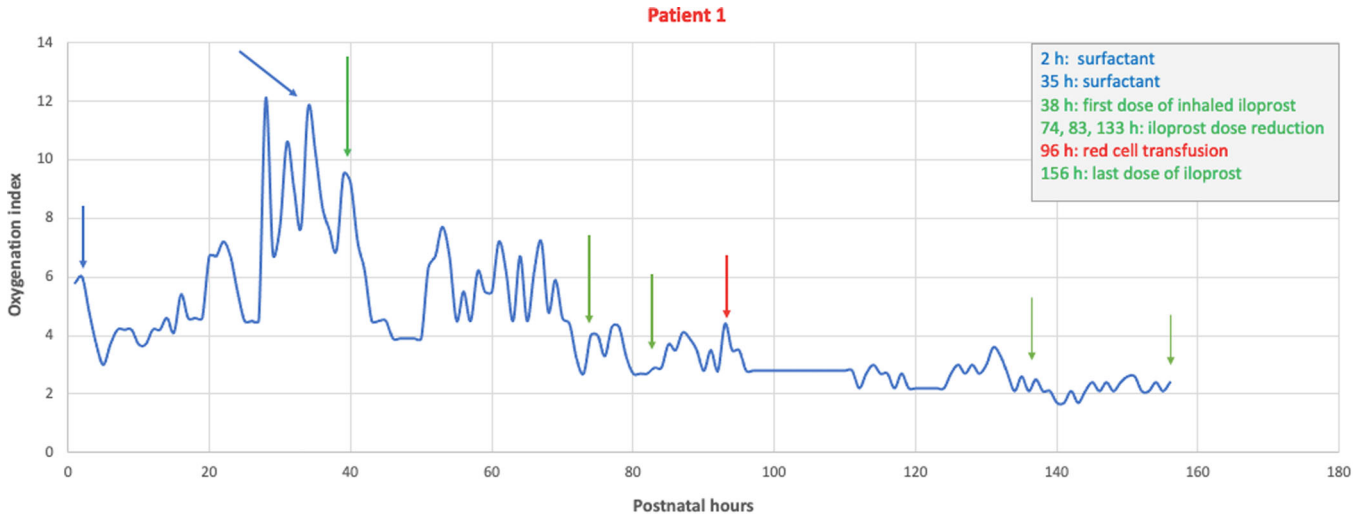

FIGURE 1 Oxygenation index of patient 1.

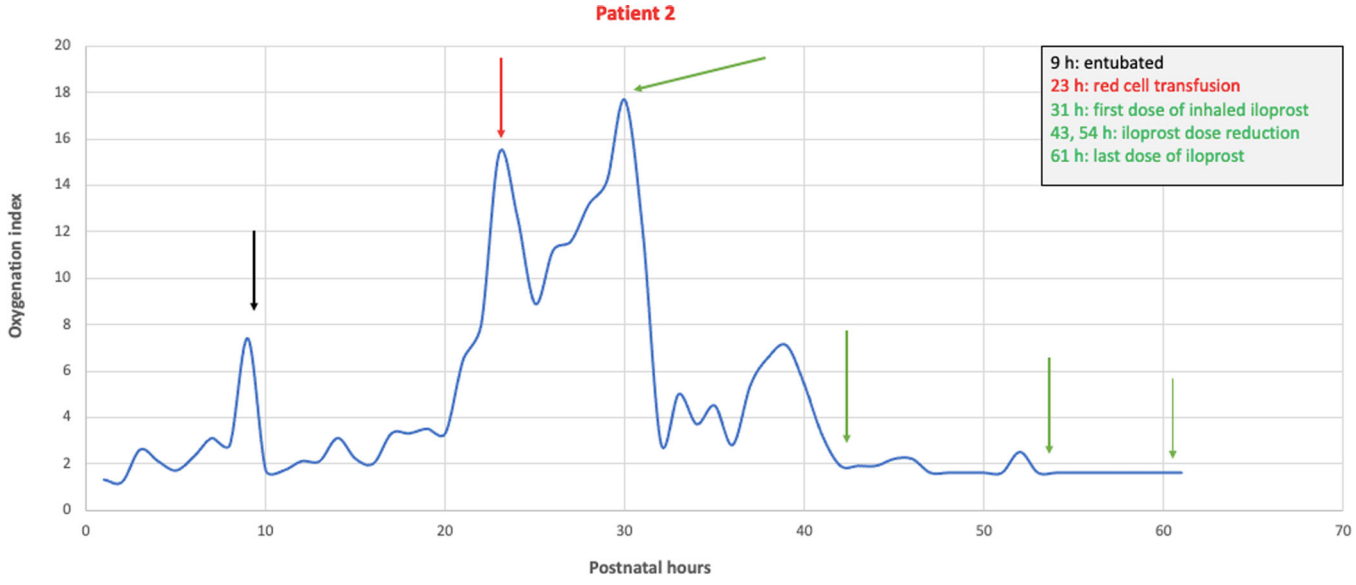

FIGURE 2 Oxygenation index of patient 2.

inhaled iloprost treatment in the absence of nitric oxide for newborns with persistent pulmonary hypertension (Supporting Information: Source file 2) by integrating a nebulizer into the ventilator circuit close to humidifier (Supporting Information: Video 1). Note that the eligibility criteria and the protocol are performed on a clinical basis in our unit, not part of a prospective research study.

Echocardiography demonstrated a right-to-left shunt or a bidirectional shunt and no structural anomaly in all patients. Immediate echocardiographic confirmation of a drop in pulmonary arterial pressure after inhaled iloprost therapy was not available but was performed during or at the end of the treatment in 5 patients (Table 1). Pulmonary arterial pressure was measured from the systolic measures from tricuspid regurgitation.

Milrinone infusion was administered to the patient 3 to alleviate the afterload because of very high ventilatory pressures, and sildenafil was to patient 5 after a rising oxygenation index due to 4 mcg/dose of iloprost.

Inhaled iloprost was escalated to 4 mcg/dose for patients 3 and 5 after the initial dose because of failure to respond to 2 mcg/dose. The sequence of therapies that might affect the oxygenation index during the treatment is also revealed (Figures 1–6).

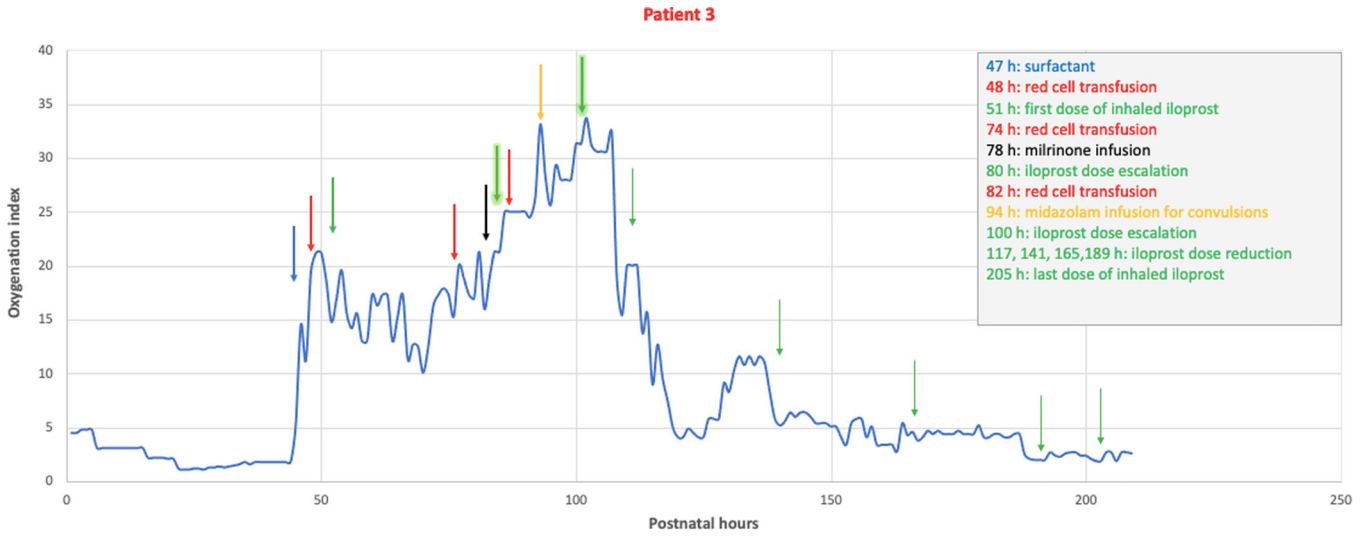

FIGURE 3 Oxygenation index of patient 3.

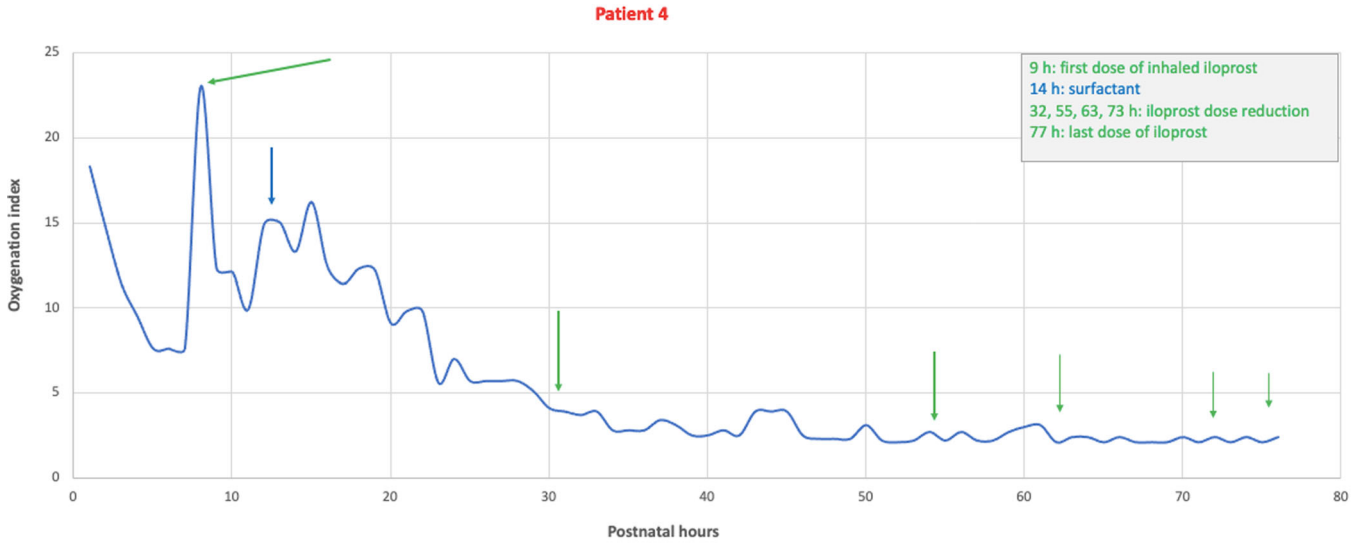

FIGURE 4 Oxygenation index of patient 4.

RESULTS

Inhaled iloprost decreased fiO_2 and improved oxygen saturation in all patients (Table 1, Figures 1–6). The only issue to consider about the therapy was the fluctuations in the oxygenation index. (Figures 1–6). No side effects were attributable to inhaled iloprost, and no mortality was recorded.

DISCUSSION

iNO is the only approved therapy for PPHN.[8] In Turkey, iNO is delivered by a private company. Sometimes the devices are occupied, so alternative treatments have to be considered now and then. Inhaled iloprost is suggested as a sole or adjunctive therapy in the literature. It is readily available and has comparable clinical effects to iNO.[20–35] Due to ethical issues, conducting randomized trials of inhaled iloprost is challenging, so the clinical experience has gained prominence.

In terms of dosage and timing, there are no specific guidelines for the inhaled treatment of iloprost. It has a biological half-life of 20−30 min in humans.[36] For the treatment of adult PAH, a dose of 2.5−7.5 mcg, 6−9 times a day, with a maximum amount of 45 mcg per day, was approved in 2004.[37] The same doses are used in children with success.[38] For neonates, different dosages are suggested in the literature;

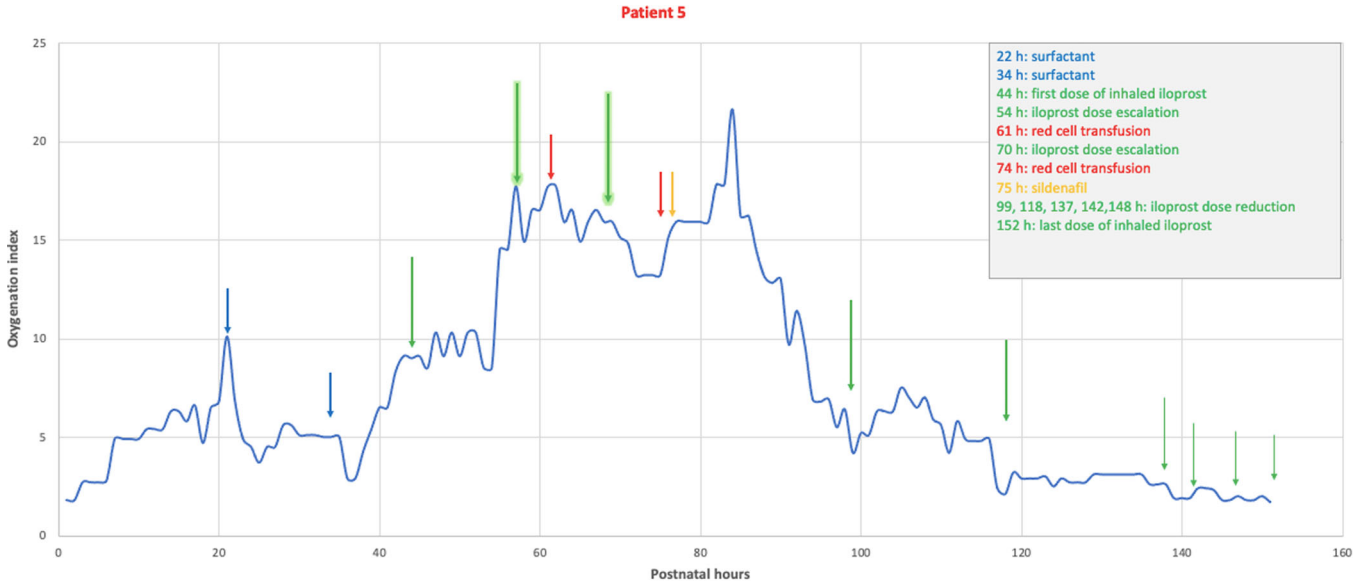

FIGURE 5 Oxygenation index of patient 5.

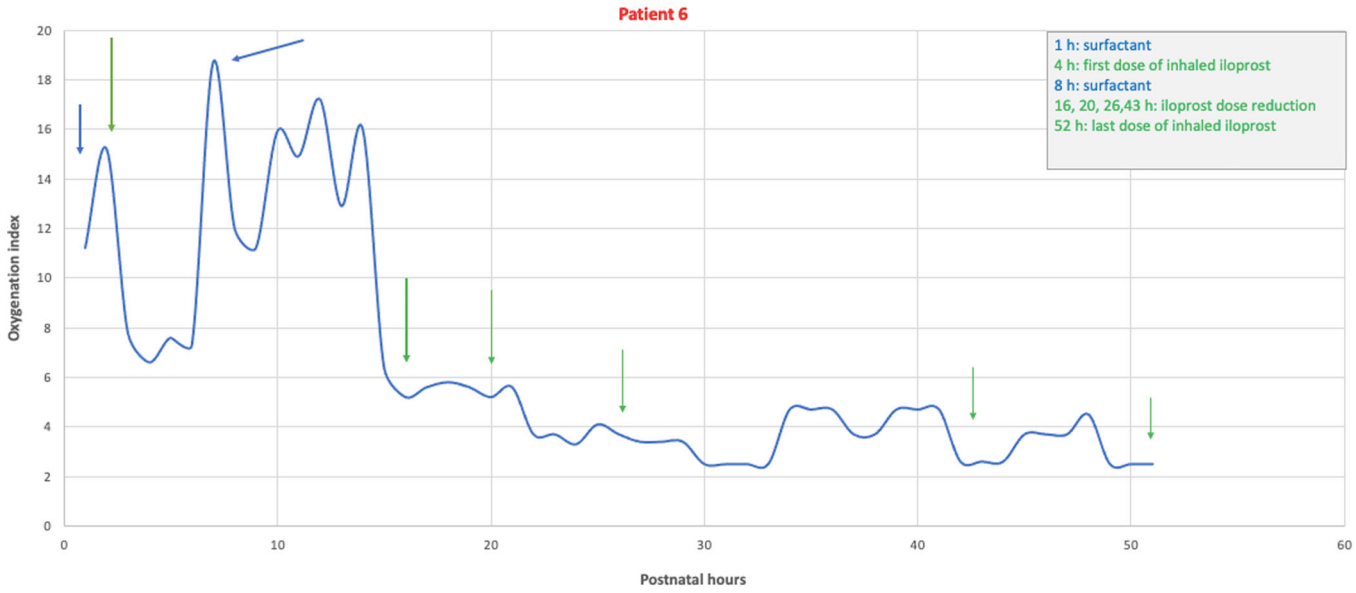

FIGURE 6 Oxygenation index of patient 6.

0.2−2.5 mcg/kg/dose every 1−6 h in general.[19–35] A report of continuous inhalation has also been made.[33] Delivering one dose of inhalation lasts approximately 5 min in our setting, and the clinical effect lasts 1−2 h at most at the beginning of treatment. Unfortunately, this causes unstable oxygen saturation. To avoid this instability, the caregiver has to react quickly to fiO_2 and oxygen saturation and decide the dosing interval. Although preferable, continuous inhalation was impossible in this setting. Techniques needed to be developed to give constant inhalation and increase the dosage, like iNO, which could provide a more stable oxygen saturation and hemodynamics. Another issue to consider is the imprecision of the actual amount of the drug delivered to the baby using an integrated nebulizer to the ventilator circuit. A certain amount may be lost in the setting. Also, all the patients mentioned above have somewhat gone through acute or chronic hypoxia and developed PPHN due to acute pulmonary vasoconstriction or pulmonary vascular remodeling mechanisms. It needs to be clarified if it works for PPHN caused by other reasons.[1,4–6]

As for the side effects, headache, cough, and dizziness were reported in adults and children

receiving inhaled iloprost. Also, intravenous iloprost was reported to cause hypotension.[39,40] For the neonates, no side effects attributable to inhaled iloprost were reported.[19–35] A maximal dose of 192 mcg/day and a cumulative dose of 510 mcg/day caused no side effects in our patients, which means very high maximal doses compared to adults are well tolerated in neonates. Two patients received inotrope for hypotension but were already on inotropic support before iloprost. Another two had inotropes to raise the mean arterial pressure to pulmonary arterial pressure, not because of iloprost-induced hypotension. So, we concluded that the adverse effects of inhaled iloprost are negligible in the neonatal population.[19–35]

Inhaled iloprost is a reliable alternative for infants with persistent pulmonary hypertension when iNO is unavailable and may be used as adjunctive therapy along with other pulmonary vasodilators.[20–35] Compared to iNO, the pros of inhaled iloprost are the lower cost and availability, and the cons are swings in oxygenation (Figures 1–6). In conclusion, our clinical experience supports that inhaled iloprost might be an alternative drug treatment for PPHN and provides safety and efficacy data that is insufficient for now in the literature. Well-designed trials are warranted to remedy the lack of evidence.

AUTHOR CONTRIBUTIONS

Only one author and no guarantor. I declare that I participated in the design, execution, and analysis of the paper by Sukran Yildirim entitled "Inhaled iloprost is an effective alternative therapy for persistent pulmonary hypertension in newborns" that I have seen and approved the final version and that it has neither been published nor submitted elsewhere. I also declare that I have no conflict of interest other than any noted in the cover letter to the editor.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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