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RESEARCH ARTICLE

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Safety and tolerability of continuous inhaled iloprost in critically ill pediatric pulmonary hypertension patients: A retrospective case series

Elizabeth Colglazier[1] | **Angelica J. Ng**[2,3] | **Claire Parker**[1] | **David Woolsey**[4] | **Raymond Holmes**[4] | **Allison Dsouza**[1] | **Jasmine Becerra**[5] | **Leah Stevens**[5] | **Hythem Nawaytou**[5] | **Roberta L. Keller**[5] | **Jeffrey R. Fineman**[5,6]

[1]Department of Nursing, University of California, San Francisco, San Francisco, California, USA

[2]Department of Pharmaceutical Services, University of California, San Francsico, San Francisco, CA, USA

[3]Merck Sharp & Dohme LLC, Rahway, New Jersey, USA

[4]Department of Respiratory Therapy, University of California San Francisco Benioff Children's Hospital, San Francisco, California, USA

[5]Department of Pediatrics, University of California San Francisco Benioff Children's Hospital, San Francisco, California, USA

[6]Cardiovascular Research Institute, University of California San Francisco Benioff Children's Hospital, San Francisco, California, USA

Correspondence
Jeffrey R. Fineman, UCSF Department of Pediatrics, 550 16th St, 5th Floor, San Francisco, CA 94143, USA.
Email: jeff.fineman@ucsf.edu

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Abstract

Inhaled iloprost (iILO) has shown efficacy in treating patients with hypoxic lung disease and pulmonary hypertension, inducing selective pulmonary vasodilation and improvement in oxygenation. However, its short elimination half-life of 20–30 min necessitates frequent intermittent dosing (6–9 times per day). Thus, the administration of iILO via continuous nebulization represents an appealing method of drug delivery in the hospital setting. The objectives are: (1) describe our continuous iILO delivery methodology and safety profile in mechanically ventilated pediatric pulmonary hypertension patients; and (2) characterize the initial response of iILO in these pediatric patients currently receiving iNO. Continuous iILO was delivered and well tolerated (median 6 days; range 1–94) via tracheostomy or endotracheal tube using the Aerogen® mesh nebulizer system coupled with a Medfusion® 400 syringe pump. No adverse events or delivery malfunctions were reported. Initiation of iILO resulted in an increase in oxygen saturation from 81.4 ± 8.6 to $90.8 \pm 4.1\%$, $p < 0.05$. Interestingly, prior iNO therapy for >1 day resulted in a higher response rate to iILO (as defined as a $\geq 4\%$ increase in saturations) compared to those receiving iNO <1 day (85% vs. 50%, $p = 0.06$). When the use of iILO is considered, continuous delivery represents a safe, less laborious alternative and concurrent treatment with iNO should not be considered a contra-indication. However, given the retrospective design and small sample size, this study does not allow the evaluation of the efficacy of continuous iILO on outcomes beyond the initial response. Thus, a prospective study designed to evaluate the efficacy of continuous iILO is necessary.

KEYWORDS
Iloprost, prostacyclin, pulmonary hypertension, pulmonary vascular disease

lloprost (Ventavis®; Actelion Pharmaceuticals) is a stable prostacyclin analog that is delivered via inhalation or intravenous (IV) for the treatment of pulmonary hypertension (PH).[1] Iloprost has a mechanism of action comparable to other prostacyclin analogues with vasodilatory and vascular remodeling effects on the pulmonary vasculature.[2] Inhaled iloprost (iILO) has shown efficacy in treating neonates, infants, children, and adults with hypoxic lung disease and PH.[2–14] iILO causes selective pulmonary vasodilation, limiting the systemic hypotension that may occur with systemic prostacyclin delivery. Additionally, iILO is not associated with the other serious drawbacks associated with subcutaneous (SC) and IV prostacyclins, such as site pain and central venous catheter malposition, infection, and thrombosis.[3,7]

The elimination half-life of iloprost is 20–30 min, and pharmacodynamic effects of iILO may be observed up to 30–90 min following a single inhaled dose.[1] Thus, when utilized for sub-acute or chronic therapy, it requires frequent administration, at least 6–9 times daily.[3,7,15] iILO is typically delivered via the I-NEB adaptive aerosol delivery (ADD) system, but the effectiveness of iILO with various types of nebulization devices has also been described.[7,8,16] The most common side effects associated with iILO administration include cough, headache, flushing, jaw pain, bronchoconstriction, and systemic hypotension.[3,4]

Given the short elimination half-life of Iloprost, some patients may require a more sustained response and more frequent dosing. Thus, the administration of iILO via continuous nebulization represents an appealing method of drug delivery in the hospital setting. Yet only a very limited number of case studies describe the use of continuous iILO for critically ill patients with pulmonary vascular disorders.[8,11,17] In addition, although acute administration of iILO and inhaled nitric oxide (iNO) have shown similar pulmonary vasodilating effects with minimal synergistic effects when co-administered,[18–23] the response to iILO coadministration following ongoing iNO administration has not been reported. Since cross-talk between NO-mediated cGMP production and prostacyclin-mediated cAMP production is well described, the potential additive effect of iILO during ongoing iNO administration warrants investigation.[24]

The objectives of this report are to: (1) describe our continuous iILO delivery methodology and safety profile in critically ill, mechanically ventilated neonatal and pediatric PH patients, (2) characterize the initial response (30 min) of iILO in these pediatric patients currently receiving iNO; and (3) evaluate the potential effect of the duration of iNO use before iloprost with the response to iloprost.

METHODS

This retrospective case series was approved by the University of California San Francisco (UCSF) Medical Center investigational review board. Patients were identified through a review of the UCSF pediatric PH database. Between 2017 and 2022, 24 patients receiving mechanical ventilation with iNO in the pediatric intensive care unit (PICU), pediatric cardiac intensive care unit (PCICU), or the intensive care nursery (ICN) received continuous iILO with 27 events of use (one patient received continuous iILO on four different occasions). In general, the PH service recommends iILO in critically ill pediatric patients as a means of providing prostacyclin therapy as either a temporary need for increased PH therapy that targets this pathway and/or as a bridge toward achieving higher dose systemic parenteral therapy. Before initiation of continuous iILO, a test dose of 2.5–5 μg was given. Demographic and clinical data, including potential adverse events and cardiopulmonary data just before and within 30 min following the test dose was collected. Values are presented as mean ± SEM. Pre and postiloprost cardiopulmonary data was compared using the paired *t*-test. Comparisons between the duration of iNO therapy before iILO with the response to iILO were made with the chi-squared test. For this analysis, an increase in systemic oxygen saturation of 4% or greater, as determined by pulse oximetry, was considered a positive response to iILO. The response of 4% was empirically chosen after looking at the distribution of the increase in saturation across the 27 events. It was determined that there was a clear clustering around 0%–2% saturation change for nonresponders, and >4% for responders. In addition, this value approximates the median change. A p value < 0.05 was considered significant.

Continuous inhaled iloprost preparation and delivery

Continuous iILO was delivered to patients via tracheostomy or endotracheal tube using the Aerogen® vibrating mesh nebulizer system (Aerogen®) coupled with a Medfusion® 400 (Smiths Medical, Inc.) syringe pump (Figure 1). Iloprost solutions were compounded aseptically by pharmacy staff and dispensed in proprietary Aerogen® syringes clearly labeled with "For Inhalation Only" stickers to prevent inadvertent IV administration. Iloprost was prepared in a 1 μg/mL concentration for the earlier cohort of patients. However, as it became apparent that a certain subset of patients required Iloprost doses higher than 10 mcg/h, the concentration was increased to 2 μg/mL. This was done to align with the Aerogen® manufacturer's recommendations of a maximum medication rate of 12 mL/h. To minimize

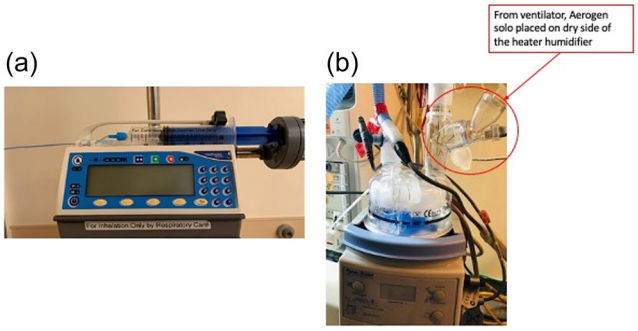

FIGURE 1 Continuous Inhaled Iloprost Delivery System. An Aerogen® mesh nebulizer system (a, Aerogen®) is coupled with a Medfusion* 400 (b, Smiths Medical, Inc.) syringe pump. Iloprost solutions were compounded aseptically by pharmacy staff and dispensed in proprietary Aerogen® syringes clearly labeled with "For Inhalation Only" stickers to prevent inadvertent IV administration. Iloprost was prepared in a 1–2 μg/mL concentration. To minimize the risk of interruptions to iloprost delivery, the Aerogen® device was inspected hourly by respiratory therapists to ensure that there were no device malfunctions, and that the fill rate of the iloprost solution did not exceed the output rate of the nebulizer. Iloprost solution syringes were changed every 4 h.

the risk of interruptions to iloprost delivery, the Aerogen® device was inspected hourly by respiratory therapists to ensure that there were no device malfunctions, and that the fill rate of the iloprost solution did not exceed the output rate of the nebulizer. Due to the paucity of published stability data, 2 μg/mL iloprost solution syringes were changed every 4 h.

In general, once deemed clinically appropriate to discontinue iILO (improved cardiopulmonary hemodynamics and/or achieved goal parenteral prostacyclin dosing), the continuous dose was initially weaned. If tolerated, then intermittent dosing was attempted; initially every 2 h and then every 4 h. Following every 4 h dosing, iILO was switched to as needed. Safety was assessed as any adverse event that could be attributed to iILO use. Tolerability was defined by the need for additional therapies (i.e. bronchodilators) related to iILO use or the need to discontinue iILO therapy for potential adverse effects.

RESULTS

Between January 2017 and December 2022, continuous iILO was utilized 27 times in 24 patients. Patient ages ranged from 2 weeks to 14 years (median age 0.58 years). Fourteen of 24 patients (58%) were female, and 11/24 (45.8%) were classified as WHO PH Group 1.[25] All patients were mechanically ventilated with New York Heart Association Functional Class IV (100%) and were being treated with iNO. All patients were considered to have severe pulmonary vascular disease and/or refractory hypoxemia, based on clinical criteria (including invasive hemodynamics), recent cardiac catheterization, or echocardiogram. General demographics are reported in Table 1; diagnosis and reason for iILO initiation are reported in Table 2. Reasons for initiation of iloprost included clinical deterioration due to an intercurrent Illness (6/27, 22.2.%), disease progression (18/27, 66.7%), and anesthesia/procedure recovery (3/27, 11.1%) (Table 2). All patients were concurrently receiving iNO (20–40ppm) for a median duration of 4 days (range 1–89 days) before the administration of iILO. Other PH medications concurrently administered included phosphodiesterase V inhibitors (14/24, 58.3%), endothelin receptor antagonists (17/24, 70.8%), and treprostinil IV/SQ (11/24, 45.8%). The clinical deterioration in five of these patients required ECLS (5/27, 18.5%).

TABLE 1 Patient demographics.

Demographics	All patients ($n = 24$)
Sex, female, *n* (%)	14 (58%)
Age at diagnosis (years)	
Median	0.58
Range	0.08–14.2
PH WHO Group Classification, *n* (%)	
PH Group 1	11 (45.8%)
PH Group 2	2 (8.3%)
PH Group 3	11 (45.8%)
PH Group 4	0 (0%)
PH Group 5	0 (0%)
Trisomy 21, *n* (%)	4 (16.7%)
NYHA Functional Class, *n* (%)	
FC I	0 (0%)
FC II	0 (0%)
FC III	0 (0%)
FC IV	24 (100%)

Abbreviation: PH, pulmonary hypertension.

Acute response to inhaled iloprost

Before initiating continuous therapy, all patients received a "test dose" (2.5–5.0 μg) of iILO. Initiation resulted in an increase in oxygen saturation from 81.4 ± 8.6 to 90.8 ± 4.1%, $p < 0.05$. Heart rate (from 150.9 ± 5.2 to

TABLE 2 Patient diagnosis and reason for continuous inhaled iloprost.

Diagnosis	Reason for continuous inhaled iloprost
Group 1 ($n = 11$)	
PPHN ($n = 2$)	Disease progression ($n = 2$)
CHD ($n = 4$)	Disease progression ($n = 3$)
	Anesthesia recovery, s/p AV canal repair ($n = 1$)
CHD + T21 ($n = 1$)	Intercurrent illness ($n = 1$)
Heritable ($n = 2$)	Disease progression ($n = 1$)
	Intercurrent illness ($n = 1$)
Portal HTN ($n = 1$)	Disease progression ($n = 1$)
Connective tissue ($n = 1$)	Disease progression ($n = 1$)
Group 2 ($n = 2$)	
Shone's complex ($n = 2$)	Disease progression ($n = 1$)
	Anesthesia recovery, s/p heart transplant ($n = 1$)
Group 3 ($n = 11$)	
BPD ($n = 3$)	Intercurrent illness ($n = 2$)
	Anesthesia recovery ($n = 1$)
BPD + CHD + T21 ($n = 3$)	Intercurrent illness ($n = 3$)
CDH ($n = 2$)	Disease progression ($n = 1$)[a]
	Anesthesia recovery ($n = 1$)
ACDMPV ($n = 2$)	Disease progression ($n = 2$)
ACDMPV + CHD ($n = 1$)	Disease progression ($n = 1$)

Note: Group, PH diagnostic classification group.

Abbreviations: ACDMPV, alveolar capillary dysplasia misaligned pulmonary veins; BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; PPHN, persistent pulmonary hypertension of the newborn.

[a]While $n = 1$, patient has four separate instances of continuous inhaled iloprost recorded in the data set.

141.7 ± 13.1 beats/min) tended to decrease, while systolic (from 81.5 ± 4.2 to 85.7 ± 4.6 mmHg) and diastolic blood pressures (from 44.7 ± 3.1 to 49.6 ± 3.4 mmHg), and cerebral near-infrared spectroscopy (NIRS, from 60.7 ± 4.0 to 69.2 ± 3.3, $n = 11$) tended to increase, but these parameters did not reach statistical significance (Figure 2). Interestingly, of the 14 patients who had been treated with iNO for greater than one day before the iILO challenge, 12 had a positive response (85.7%). In comparison, only 5 of the 10 patients treated with iNO for less than 1 day responded (50.0%, $p = 0.06$). In fact, the median increase in oxygen saturation in response to iILO in those patients treated with iNO for >1 day was 11% (range 0%–65%), compared with a 1% (range −4% to 8%) increase in those treated with iNO ≤ 1 day. Three patients were excluded from this analysis because their baseline saturation was 97% or greater.

Continuous iloprost administration

Following the initial test dose, all patients were initiated on continuous iloprost inhalation. The median duration of continuous iloprost was 6 days (range 1–94 days). The median dose was 7.5 μg/h (range 2.5–15.0 μg/h). All patients were concurrently receiving iNO (20–40 ppm) for a median duration of 4 days (range 1–89 days) before the administration of iILO. Bronchodilators were co-administered in 23 of the 27 iILO administrations (85.2%). A subset was started empirically with the initiation of iloprost, while others were previously on bronchodilators for lung disease. No patient required an increase in bronchodilator therapy following initiation of iILO.

Outcomes

The continuous administration of iILO was well tolerated in all cases. No adverse effects were associated with its delivery. In particular, bronchoconstriction requiring additional bronchodilator therapy, bleeding, or systemic hypotension were not reported. Eleven of the 24 patients (45.8%) died during their hospitalization. Five of 11 died while receiving continuous iILO, which included two patients with alveolar capillary dysplasia (ACD), one patient with persistent pulmonary hypertension of the newborn (PPHN), one patient with severe bronchopulmonary dysplasia (BPD) during an intercurrent illness, and one patient with newly diagnosed heritable pulmonary arterial hypertension (PAH) who presented following a prolonged cardiopulmonary arrest. The remaining six of the 11 deaths occurred after iILO administration was discontinued. No deaths were secondary to refractory right ventricular failure, and 10/11 deaths were associated with a re-direction of care toward comfort. Of the 13 patients who were discharged home, 11 (84.6%) were discharged on increased PH medications, and two were discharged on their baseline PH medication. Increased PH medications included the new administration of SQ or IV treprostinil in 9 (81.8%) of the 11.

Five patients had iILO initiated while on ECLS. None of these patients had been previously treated with a prostacyclin, and all were felt to require prostacyclin therapy to stabilize before cannulation ($n = 2$) and/or facilitate ECLS separation ($n = 5$). Thus, iILO was initiated as a bridge during initiation and rapid titration

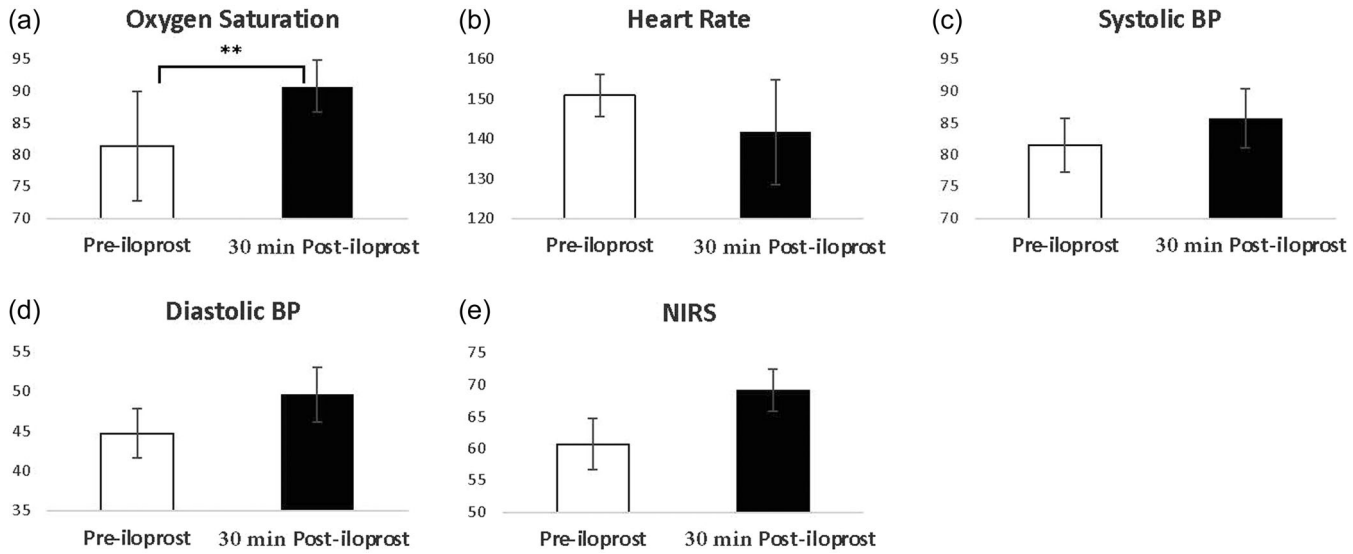

FIGURE 2 Acute response to inhaled iloprost. All patients received a "test dose" (2.5–5.0 μg) of inhaled iloprost. Initiation (30 min after the dose) resulted in an increase in oxygen saturation (a) from 81.4 ± 8.6 to 90.8 ± 4.1%, $p < 0.05$. Heart rate (b) (from 150.9 ± 5.2 to 141.7 ± 13.1 beats/min) tended to decrease, while systolic (c) (from 81.5 ± 4.2 to 85.7 ± 4.6 mmHg) and (d) diastolic blood pressures (from 44.7 ± 3.1 to 49.6 ± 3.4 mmHg), and near-infrared spectroscopy (e) (NIRS, from 60.7 ± 4.0 to 69.2 ± 3.3, $n = 11$) tended to increase, but these parameters did not reach statistical significance. Values are mean ± SEM. **$p < 0.05$. SEM, standard error of mean.

of treprostinil therapy (which can be limited by systemic hypotension), in attempt to facilitate ECLS separation before achieving an adequate parenteral Treprostinil dose. Four of the 5 (80%) patients in which iILO was initiated were able to separate from ECLS. One patient, a newborn with obstructed TAPVR who was cannulated for supra-systemic PH and low cardiac output following repair at an outside hospital, did not separate from ECLS. The patient was empirically started on iILO on admission to our hospital to facilitate systemic parenteral treprostinil initiation and titration. However, further evaluation revealed significant neurologic injury and persistent obstructed veins, and care was re-directed toward comfort. Three patients (two s/p corrective cardiac surgery, and one newly diagnosed with systemic sclerosis) had iILO discontinued following ECLS decannulation and were discharged on systemic parenteral treprostinil. One patient, chronically on dual enteral therapy following AV canal repair, suffered a cardiac arrest at an outlying hospital secondary to an unrecognized GI bleed. This child was transferred to our hospital following cannulation to ECLS. In the setting of severe acidosis, iILO was empirically started on admission for evidence of severe right heart dysfunction, while initiation and up-titration of systemic parenteral treprostinil occurred. However, following treatment for the GI bleed and decannulation, both prostacyclin therapies were able to be discontinued, and she was discharged on her home PH regimen.

DISCUSSION

This report represents the first case series on the use of continuous iILO in critically ill pediatric PH patients. Utilization included a bridge of support during initiation and/or up-titration of parenteral prostacyclin therapy, support to separate from ECLS, and support during acute exacerbations secondary to disease progression and/or intercurrent illnesses. Importantly, continuous inhaled administration over several days was well-tolerated, and its use was not associated with any adverse events, serious equipment malfunctions, or systemic prostacyclin side effects. Before initiation of iILO continuous delivery, all patients received an initial test dose, which was associated with a significant increase in oxygen saturation, and trends toward improvement in indirect indices of cardiac output, such as decreases in heart rate, and increases in systemic blood pressure and NIRS. Given the retrospective nature and sample size of this report, efficacy of continuous iILO in this complex, dynamic patient population cannot be evaluated.

Several adult studies demonstrate efficacy of chronic intermittent iILO for PAH, particularly when administered as add-on and/or combination therapy,[4,7,13,15] with positive primary endpoints of improvement in functional class, 6-min walk test, and cardiopulmonary hemodynamics. In these studies, iILO was delivered 6–9 times daily with reasonable compliance.[4,7,13,15] Pediatric studies are limited. Ivy et al.[3] report the largest pediatric

cohort with 23 patients with Group 1 PAH. Dosing (2.5–10 μg) was administered 4–9 times daily. Although approximately 35% demonstrated improved functional class after 6 months, iILO was discontinued in 36% due to airway reactivity, worsening clinical status, or death. In addition, a few pediatric case reports include the use of chronic intermittent iILO to avoid parenteral prostacyclin therapy, and as a bridge to transplant.[26–28] The majority of the pediatric in-patient delivery of intermittent iILO is in PPHN and the postoperative congenital heart surgical populations.[5,8,9,11,12,16,18,19,21,29] This includes iILO administration via noninvasive ventilation, conventional positive pressure ventilation, and high-frequency ventilation. Iloprost administration generally resulted in improvement in saturations, and cardiopulmonary hemodynamics, including right ventricular function when evaluated.[5,8,9,11,12,16,18,19,21,29] In all these studies, potential effect on long-term outcomes could not be determined.

The largest report of continuous delivery of iILO is in adults following cardiothoracic surgery.[8] Administration averaged 45 h in 126 adults with a maximum time of 16 days. Pediatric experience is limited to two case reports; a newborn with PPHN who received continuous delivery for approximately 1–2 days, and a newborn following corrective surgery for D-TGA, who received delivery for 18 days at a dose of 5 μg/h.[11,17] In these reports, no adverse effects were attributed to the administration. We describe a median peak dosage of continuous iILO dose of 7.5 μg/h (range of 2.5–20 μg/h) and utilization 1–94 days (median 6 days) with no adverse effects. The current report clearly represents the largest pediatric experience with continuous iILO administration and contains administration for up to 94 days. Like these previous limited reports, we did not encounter any adverse effects from continuous delivery, although almost all children had contemporaneous administration of bronchodilators.

Several studies have compared the acute cardiopulmonary effects of iILO with iNO.[18–22] This includes vasoreactivity testing in the cardiac catheterization laboratory, and postoperative PH management. Most have demonstrated similar pulmonary vasodilating responses between iNO and iILO, and minimal additive effects when co-administered.[18–22] Interestingly, in the current report, we saw an improvement in oxygen saturation with iILO administration despite being concurrently treated with iNO. In fact, as opposed to simultaneous acute testing investigations, all of our patients had been previously treated with iNO (a median of 4 days, range 1–89 days), before iILO administration. Cross-talk between NO-generated cGMP and prostacyclin-generated cAMP has been well described.[24] In fact, NO exposure in pulmonary artery smooth muscle cells results in a cGMP-mediated increase in PDE3 protein expression and activity. PDE3 is an enzyme system that catalyzes the hydrolysis of cAMP, resulting in decreased cAMP levels. Thus, theoretically, chronic iNO exposure may decrease cAMP levels in patients, "priming" the vasculature for a positive response to iILO, which may not occur following acute iNO coadministration. Interestingly, in the current study, patients who had been receiving iNO for greater than one day were more apt to respond to iILO than those exposed to iNO for less than one day, but this trend did not reach statistical significance (85.7 vs. 50.0%, $p = 0.06$). It is also noteworthy that most of these patients were concurrently being treated with PDE5 inhibitors and/or exogenous prostacyclin therapy, which should also influence cGMP and cAMP levels, respectively. The hypothesis that previous/concurrent treatment of these agents could alter responsiveness by cAMP/cGMP cross-talk is intriguing and warrants further in vivo investigation. However, our experience suggests that concurrent treatment with iNO should not be considered a contraindication to attempting iILO treatment.

Inhaled prostacyclins offer an appealing option for the treatment of PH given their selective pulmonary vasodilating effect during an acute illness. Iloprost is one of only two prostacyclins approved by the Food and Drug Administration (FDA) for inhalation use in the United States.[2] Treprostinil (Tyvaso, United Therapeutics) is administered via specific inhalation systems, and at the time of this publication there is only limited data on the delivery of inhaled treprostinil during mechanical ventilation,[30] and there are no reports describing the use of continuous inhaled treprostinil. On the other hand, epoprostenol has been approved for continuous IV infusions, and the IV formulations have been aerosolized and administered continuously as an off-label medication in critically ill adults and children.[31,32] However, to remain stable, epoprostenol is diluted in a buffered solution (glycine buffer or arginine buffer) that is designed for IV administration, not inhalation. It is unknown whether inhalation of a buffered epoprosentol causes airway alkalinization and lung injury in humans.[33] Additionally, aerosolized epoprostenol has been shown to clog ventilator valves.[8] Thus, iILO represents an ideal option for continuous inhaled use, and has been effectively administered via nebulizer to infants through conventional mechanical ventilation and high-frequency oscillatory ventilation (HFOV).[16]

Limitations of this report are noteworthy, particularly its retrospective nature and small sample size. Thus, the potential benefits on patient outcome cannot be delineated. In fact, 11 of the 24 (45.8%) of this cohort died during their hospitalization. However, the cohort was a particularly critically ill population with 3 patients

suffering from ACD, a lethal developmental lung disease[34] and all patients required mechanical ventilation. Morrell et al. demonstrated that pediatric pulmonary hypertensive patients admitted to a cardiac intensive care unit who required invasive mechanically ventilation were at increased risk for mortality.[35] Thus, given the likely selection bias of administering iILO continuously in the sickest patients, this high mortality is not unexpected. In addition, it should be noted that many of the potential side effects (i.e., headache, jaw pain, and cough) could not be adequately assessed in sedated, intubated patients. Lastly, this report focuses on the safety and tolerability of continuous iILO therapy; the important question of longer-term outcomes beyond the initial response cannot be extrapolated.

Iloprost is a commonly added PH therapy in critically ill pediatric patients. Indications include a bridge during up-titration of parenteral prostacyclin therapy, support during clinical worsening secondary to disease progression or an intercurrent illness, or support to facilitate separation from ECLS.[3,7,36] However, given its short elimination rate, appropriate intermittent dosing necessitates every 1–3 h administration; 6–9 times daily which represents an enormous challenge in the pediatric population. The current report represents the only pediatric case series describing the use of continuously administered iILO. Importantly, even quite prolonged administration (94 days) appeared safe and was well-tolerated, and continuous iILO was never discontinued because of adverse effects. In addition, despite ongoing iNO delivery, initiation of iILO resulted in an improvement in oxygen saturation and trends toward improvement in hemodynamics. Thus, when the use of iILO is considered, particularly as a bridge to systemic parenteral prostacyclin initiation and/or rapid up-titration which may be limited by systemic hypotension, continuous delivery may represent a safe, less laborious alternative. Prospective studies on the use of continuous iILO in critically ill pediatric PH patients are needed to better determine the effect on patient outcomes.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception of the work; revising the work critically for important intellectual content; have approved the final version to be published; and agree to be 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.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This work was performed under Institutional IRB approval.

ORCID

Jeffrey Fineman http://orcid.org/0000-0001-9740-405X

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