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ORIGINAL PAPER

Comparison of inhaled nitric oxide with aerosolized iloprost for treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery

Tsvetomir Loukanov · Dietrich Bucsenez · Wolfgang Springer · Christian Sebening · Helmut Rauch · Eva Roesch · Matthias Karck · Matthias Gorenflo

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Abstract
Objectives Pilot study to compare the effect of inhaled nitric oxide (iNO) and aerosolized iloprost in preventing perioperative pulmonary hypertensive crises (PHTCs).
Background Guidelines recommend the use of iNO to treat PHTCs, but treatment with iNO is not an ideal vasodilator. Aerosolized iloprost may be a possible alternative to iNO in this setting.
Methods Investigator-initiated, open-label, randomized clinical trial in 15 infants (age range 77–257 days) with left-to-right shunt (11 out of 15 with additional trisomy 21), and pulmonary hypertension (i.e. mean pulmonary artery pressure [PAP] >25 mmHg) after weaning from cardiopulmonary bypass. Patients were randomized to treatment with iNO at 10 ppm or aerosolized iloprost at 0.5 μg/kg (every 2 h). The observation period was 72 h after weaning from cardiopulmonary bypass. The primary endpoint was the occurrence of PHTCs; the secondary endpoints were mean PAP, duration of mechanical ventilation, safety of administration, and in-hospital mortality.
Results Seven patients received iNO and eight patients received iloprost. During the observation period, 13 of the 15 patients had at least one major or minor PHTC. There was no difference between the groups with regard to the frequency of PHTCs, mean PAP and duration of mechanical ventilation ($p > 0.05$).
Conclusions In this pilot study, aerosolized iloprost had a favorable safety profile. Larger trials are needed to compare its efficacy to iNO for the treatment of perioperative pulmonary hypertension. However, neither treatment alone abolished the occurrence of PHTCs.

Keywords Congenital heart disease · Surgery · Pulmonary hypertension · Children

Abbreviations

iNO	Inhaled nitric oxide
FiO_2	Fraction of inspired oxygen
Qp/Qs	Ratio of pulmonary to systemic blood flow
$PaCO_2$	Partial arterial pressure of carbon dioxide
PaO_2	Partial arterial pressure of oxygen
PAP	Pulmonary arterial pressure
Pp/Ps	Ratio of pulmonary to systemic blood pressure
ppm	Parts per million
PVR	Pulmonary vascular resistance
PHTC	Pulmonary hypertensive crisis

T. Loukanov (✉) · C. Sebening · M. Karck
Department of Cardiac Surgery, University of Heidelberg Medical Centre, INF 110, 69120 Heidelberg, Germany
e-mail: tsvetomir.loukanov@med.uni-heidelberg.de

D. Bucsenez · W. Springer · E. Roesch · M. Gorenflo
Department of Pediatric Cardiology, University Medical Center, Heidelberg, Germany

H. Rauch
Department of Anesthesiology, University Medical Center, Heidelberg, Germany

Introduction

Infants and children with pulmonary hypertension associated with left-to-right shunt may face persistent pulmonary hypertension after intracardiac repair using cardiopulmonary bypass [1]. In its most severe form, pulmonary hypertensive crisis (PHTC), this may ultimately lead to arterial O_2 desaturation, circulatory collapse, and

even death. The frequency of PHTC in children with left-to-right shunt undergoing intracardiac repair is reported to be between 2 [2] and 5% [3]. Miller and co-workers [4] reported a mean rate of 2.9 PHTCs per patient at risk for PHTC after intracardiac repair. Patients with trisomy 21 and atrioventricular septal defect are at particular risk of developing PHTC after intracardiac repair [2]. In these patients, the prophylactic use of inhaled nitric oxide (iNO) is effective in reducing the rate of PHTC and in shortening the length of stay in intensive care [4]. Although the effect of prophylactic iNO on mortality has been a matter of debate [5, 6], European guidelines favor its use in patients with severe postoperative pulmonary hypertension [7].

Although iNO is recommended for the treatment of postoperative pulmonary hypertension, its use may not be feasible in all centers: potential issues include the risk of rebound pulmonary hypertension following withdrawal, toxicity, and cost. Inhaled prostanoids such as iloprost may provide an alternative to iNO, but few data are currently available. An observational study demonstrated effectiveness of inhaled aerosolized iloprost to reduce the frequency of PHTC in 12 children with postoperative pulmonary hypertension and PHTC [8]. Others have demonstrated in five children that aerosolized iloprost was as effective as iNO in lowering pulmonary arterial pressure (PAP) after intracardiac repair using cardiopulmonary bypass [9].

We therefore aimed to study whether aerosolized iloprost treatment of pediatric patients with left-to-right shunt undergoing intracardiac repair with cardiopulmonary bypass would be able to reduce the rate of PHTCs as effectively as iNO. We also examined whether aerosolized iloprost was as effective as iNO in reducing PAP in the first 72 h after termination of cardiopulmonary bypass, and in reducing the need for mechanical ventilation.

Methods

This study was conducted as an exploratory, investigator-initiated, proof-of-concept trial. We used an open-label, randomized study design with parallel groups. The trial was conducted in accordance with the principles governing clinical research as set out in the Declaration of Helsinki and Good Clinical Practice. The protocol was approved by the Ethical Committee of the University of Heidelberg Medical Center (L-385/2003). The study was monitored by the Center for Clinical Studies at the University of Heidelberg Medical Centre. Informed written consent was obtained from the patients' parents before inclusion. This study was performed from September 2003 until September 2008.

Patients

Children with congenital heart disease who underwent biventricular repair were eligible for enrollment if their mean PAP was more than 25 mmHg [10] immediately after weaning from cardiopulmonary bypass when having reached stable hemodynamic conditions.

Surgical management was standardized during this study. Intracardiac repair was performed through median sternotomy with standard cardiopulmonary bypass using bicaval cannulation, moderate hypothermia at 24–26°C and antegrade extracellular cardioplegia. After weaning from cardiopulmonary bypass and warming, blood pressure in the pulmonary artery and aorta was measured via invasive pressure lines connected to a hemodynamic monitoring system in all patients.

This group of patients was a subgroup of 224 patients who presented prior to intracardiac repair with left-to-right shunt and high pulmonary blood flow ($Qp/Qs \geq 1.5$) [11] associated with congenital heart disease. All patients underwent cardiac catheterization before surgery.

Patients were excluded if: they presented with atrial septal defect, cyanotic congenital heart disease, univentricular atrioventricular connexion, or valvular or subvalvular pulmonary or aortic stenosis; they required emergency cardiac surgery; or they had systemic arterial hypertension, renal failure, diabetes mellitus, or known disorders of blood coagulation and hemostasis. In addition, patients on extracorporeal membrane oxygenation before cardiac surgery and patients treated with epoprostenol were also excluded.

Treatment

Patients fulfilling the entry criteria were randomized by an independent monitor using a computer-based scheme to receive either iNO or aerosolized iloprost. After termination of cardiopulmonary bypass and measuring of baseline PA pressure, patients in the iNO group were given iNO (Westfalen-Gas, Germany) at a dose of 10 parts per million (ppm) [3] using a commercially available system for iNO application and concentration measurement (Draeger NODOMO®). Patients in the iloprost group were given iloprost (Ventavis®, Bayer Vital, Germany) at 0.5 μg/kg every 2 h for a minimum of 72 h using an ultrasound nebulizer (Nebutec). The nebulizer was connected to the distal inspiratory part of the respiratory circuit.

For both groups, the observation period ended at 72 h after termination of cardiopulmonary bypass. This was the minimum treatment time with iloprost. In the iNO group, iNO was given likewise for at least 72 h after termination of cardiopulmonary bypass if weaning was not possible. Thereafter treatment with iNO and iloprost was continued

on an individual basis as clinically required (e.g., recurrent PHTC, inability to wean from iNO).

Endpoints

The primary endpoint was the occurrence of PHTCs during the observation period. As defined by Miller 2000 [4]: major PHTC was an episode with a rise in the ratio of pulmonary to systemic blood pressure (Pp/Ps) to >0.75 as recorded by invasive arterial lines plus either a >20% decline of systemic blood pressure or a decline of oxygen saturation to <90% as measured by transcutaneous pulse oxymetry; minor PHTC was an episode with a rise in Pp/Ps to >0.75, but no concomitant decline in systemic blood pressure or oxygen saturation.

Secondary endpoints were: the cumulated mean PAP and Pp/Ps as measured with arterial lines during the period of observation; the duration of mechanical ventilation (in hours) until weaning from the respirator and the in-hospital mortality (until discharge from hospital).

Hemodynamic and respiratory monitoring

Invasive pressure lines were placed during cardiac surgery for continuous pressure registration from the pulmonary artery, superior vena cava, radial artery, and left atrium. Data were recorded using a computer-based system in the intensive care unit provided by Hellige (Germany). Cardiac output was determined every 12 h after cardiopulmonary bypass using a transpulmonary indicator dilution technique (COLD Z-021, Pulsion Medical Systems, München, Germany). In patients weighing below 10 kg, a 1.3 Fr thermistor (PV2011, Pulsion Medical Systems) was introduced through a 20 G catheter (Vygon) within the femoral artery [12]. The calculation of pulmonary vascular resistance (PVR) and systemic vascular resistance was performed according to standard formulae [13].

Arterial blood gases were checked and respiratory parameters were recorded at regular intervals (every 2 h). The ratio of partial arterial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) was calculated at regular intervals (12 h).

Standard postoperative care

All enrolled patients received the following standard postoperative care and treatment as depicted in Table 1.

Table 1 Standard postoperative care

Analgesia, sedation	Fentanyl	2–25 μg/kg/min
	Midazolam	1–4 μg/kg/min
Intermittent positive pressure ventilation	Hyperoxia	PaO_2 13.3–20.0 kPa
	Hyperventilation	pH 7.4–7.5
Inotropic support	Epinephrine	0.05–1.0 μg/kg/min
	Dobutamine	5–15 μg/kg/min
Vasodilator drugs	Milrinone	0.5–1.0 μg/kg/min
	Sodium nitroprusside	0.5–2.0 μg/kg/min

Weaning from mechanical ventilation

No attempt was made to wean the patients from the respirator during the first 24 h after cardiopulmonary bypass. Thereafter, inspiratory pressure, respirator rate and/or oxygen concentration were gradually reduced until normoxia (PaO_2 = 10–13.3 kPa) and normocapnia (partial arterial pressure of carbon dioxide ($PaCO_2$ = 4.7–6.0 kPa) were reached.

The criteria for starting the weaning from the respirator were the fulfillment of all of the following criteria: stability of hemodynamic parameters during the preceding 6 h; urine production >0.5 ml/kg/h; no acidosis on arterial blood gas analysis, i.e., pH >7.35; systemic arterial blood pressure within normal ranges for age; $PaCO_2$ < 6.0 kPa and PaO_2 > 13.3 kPa, while on synchronized intermittent mandatory ventilation with respirator rates of <8/min and FiO_2 <0.6.

The criteria for stopping the weaning from the respirator were: insufficient spontaneous breathing while on synchronized intermittent mandatory ventilation or tracheal continuous positive airway pressure leading to hemodynamic compromise; or minor or major PHTC during weaning.

Weaning from the respirator during iNO treatment

As depicted above, the first step was to reduce the inspiratory pressure, respirator rate and/or oxygen concentration to a level that resulted in normoxia and normocapnia. Then, iNO was reduced gradually (20% reduction per h) with the aim of ending iNO within 4 h. If no PHTC ensued, then sedation was stopped and once spontaneous breathing was established, the patient was extubated. In patients who showed signs of minor or major PHTC, the iNO treatment was continued for another 24 h before trying to wean from iNO again.

Weaning from the respirator during iloprost treatment

Aerosolized iloprost was started in the operation theatre after weaning from cardiopulmonary bypass, and was continued for 72 h thereafter. Weaning from the respirator was conducted independently from the aerosolized iloprost treatment. In patients who showed signs of PHTC after 72 h, aerosolized iloprost was continued until no signs of clinically relevant PHTC occurred.

Treatment of PHTC while on trial medication

Patients with PHTCs refractory to the trial treatment were treated with the combination of: fentanyl i.v. (0.005 mg/kg), intensified hyperventilation and hyperoxia (pH > 7.5; PaO_2 > 20 kPa). Patients with PHTCs refractory to this intensified treatment were treated as follows: patients on iNO received aerosolized iloprost (0.5 μg/kg/10 min) and patients on iloprost were given iNO at 20 ppm.

Statistics

Data are expressed as mean ± SD. The Fisher's exact test was used to analyze the difference in occurrence of minor or major PHTCs between the two treatment groups. Pre and postoperative hemodynamic and clinical data were compared using the Student's *t* test. Significant results were determined by $p < 0.05$.

Results

Patients

During the study period from September 2003 to September 2008, 224 patients with left-to-right shunt underwent intracardiac repair at our institution. In all, 92 patients were found to have a mean PAP >25 mmHg at cardiac catheterization before intracardiac repair. Of these, 17 patients met the entry criteria for the study (presence of pulmonary hypertension both preoperatively and immediately after weaning from cardiopulmonary bypass). Two parents denied participation, and therefore 15 patients were enrolled.

The median age at operation for intracardiac repair for the whole study cohort ($n = 15$) was 4.9 months (range 2.6–8.6 months) and their median weight was 4.8 kg (3.2–6.3 kg). All patients presented with congenital cardiac defects associated with left-to-right shunt (Table 2). Associated trisomy 21 was present in 11/15 cases. As assessed by cardiac catheterization before intracardiac repair, these patients showed pulmonary hypertension with increased pulmonary blood flow and only moderately increased PVR: the mean PAP before the operation was 47 mmHg (range 35–56 mmHg), Qp/Qs was 3.7 (2.0–6.9) and PVR index was 2.8 (1.1–5.5) $U*m^2$.

Seven patients were randomized to the iNO group and eight to the iloprost group. Demographic, clinical, and preoperative hemodynamic data of the randomized groups are given in Table 2.

Postoperative hemodynamics

Patients in both groups had postoperative PH as assessed by continuous pressure recordings. The mean PAP during the observation period is given in Fig. 1. The mean PAP did not differ between the two groups. The ratio Pp/Ps (Fig. 2) increased in both groups and did not differ between patients treated with iNO and those treated with iloprost ($p > 0.05$).

Residual left-to-right shunt was not detected in patients during echocardiographic follow-up, which was performed at regular daily intervals. Inotropic support was adjusted to ascertain normal left ventricular systolic function in each patient. The substances used primarily were dobutamine, epinephrine and milrinone, and if required, additional sodium nitroprusside. Patients in the iloprost group tended to need more inotropic agents (Table 3).

Cardiac output data as measured by thermodilution are given in Fig. 3. Cardiac output did not differ between the two treatment groups ($p > 0.05$). PVR was found to be increased in both treatment groups, but did not differ between the groups (Fig. 4; $p > 0.05$).

Occurrence of PHTCs

In patients receiving iNO, there were 26 minor PHTCs and two major PHTCs: one patient (patient 1) had two major PHTCs and five minor events and the other patients had only minor PHTCs (Fig. 5). In patients receiving aerosolized iloprost, six major PHTCs (in 3 patients) and 25 minor PHTCs (in 6 patients) were observed (Fig. 5). One patient (patient 5) showed four major and five minor PHTCs. There were no differences between the treatment groups in frequencies of PHTCs calculated with the Fisher's exact test ($p = 1.0$).

Intensified standard treatment was sufficient in all, but one case to alleviate the PHTCs. Patient 5 of the iloprost group was given additional iNO at day 2.

Weaning from respirator

None of the patients could be weaned from the respirator during the 72-h observation period after cardiopulmonary bypass. Patients on iNO were ventilated for a mean (SD) of 11.9 (4.6) days, and patients on iloprost were extubated 37.3 (48.4) days after intracardiac repair (Table 2). The large mean value in the iloprost group reflects the ventilator dependency until death of one patient (see below). The duration of ventilation did not differ between the two groups (*t* test, $p = 0.19$).

Table 2 Clinical data

Patient number	Diagnosis	Age at operation (months)	Weight (kg)	Mean PAP pre-op (mmHg)	Qp/Qs	PVRi ($U*m^2$)	Duration of mechanical ventilation (days)	Type and duration of treatment
Patients randomized to iNO								
1	AVSD, Tris 21	4.5	6.3	47	6.9	2.1	12.9	iNO 3 days
2	AVSD, Tris 21	4.5	4.3	47	2.6	2.2	6.2	iNO 5 days
3	AVSD	4.5	4.3	49	3.7	2.1	13.9	iNO2 days
4	VSD, Tris 21	6.1	6.0	54	3.2	3.0	18.2	iNO 3 days
5	VSD, Tris 21	6.5	4.7	36	2.6	3.3	5.2	iNO 3 days
6	AVSD, Tris 21	6.8	4.8	39	3.8	3.0	14	iNO 6 days
7	VSD	7.5	5.4	35	3.7	2.5	12.8	iNO 6 days
	Mean [SD]	5.8 [1.3]	5.1 [0.8]	43.9 [7.2]	3.8 [1.5]	2.6 [0.5]	11.9 [4.6]	3.9 [1.6]
Patients randomized to ILO								
1	VSD	2.6	4.1	55	3.8	3.1	5.0	ILO 4 days
2	AVSD, Tris 21	3.1	5.2	44	2.4	3.0	6.9	ILO 5 days
3	VSD, Tris 21	3.4	4.8	50	3.6	1.1	23	ILO 4 days
4	AVSD, Tris 21	3.9	4.5	36	6.3	1.7	17.7	ILO 3 days
5	Truncus art.	4.9	3.2	53	nd	nd	104	ILO 11 days
6	AVSD, Tris 21	5.5	4.7	40	6.1	1.6	125	ILO 8 days
7	AVSD, Tris 21	6.8	5.8	55	2	5.5	8.7	ILO 10 days
8	AVSD, Tris 21	8.6	5	56	2.6	4.4	7.9	ILO 5 days
	Mean [SD]	4.9 [2.1]	4.7 [0.8]	48.6 [7.7]	3.8 [1.7]	2.9 [1.6]	37.3 [48.4]	6.3 [3.0]
P value iNO versus ILO (*t* test)		0.32	0.29	0.24	0.96	0.63	0.19	0.08

art. arteriosus, *AVSD* atrioventricular septal defect, *ILO* aerosolized Iloprost, *iNO* inhaled nitric oxide, *nd* no data, *PAP* pulmonary arterial pressure, *preop* preoperative, *PVRi* pulmonary vascular resistance index, *U* wood units, *VSD* ventricular septal defect, *Tris 21* trisomy 21

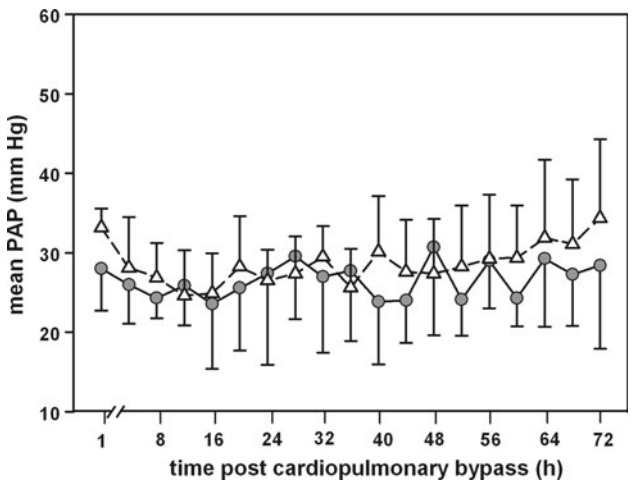

Fig. 1 The mean pulmonary arterial pressure (mean PAP) after weaning from cardiopulmonary bypass in patients treated with iNO (*gray circles*) and iloprost (*white triangles*). Data are presented as mean [SD]

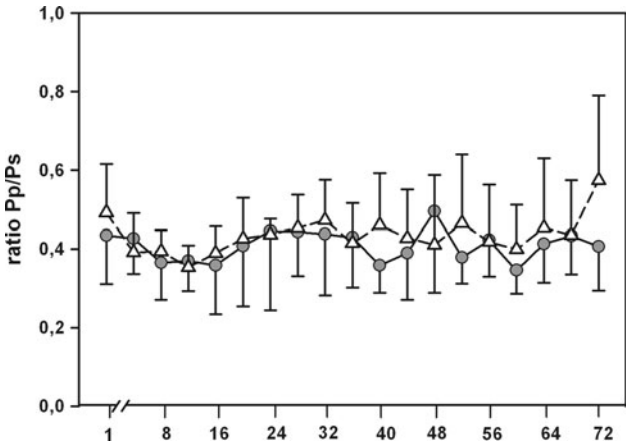

Fig. 2 The ratio of pulmonary/systemic arterial mean pressure Pp/Ps after weaning from cardiopulmonary bypass in patients treated with iNO (*gray circles*) and iloprost (*white triangles*). Data are presented as mean [SD]

Blood gas measurements

The ratio of PaO_2 to FiO_2 was slightly lower in patients treated with iloprost than in those treated with iNO, but this difference was only statistically significant at 12 h after cardiopulmonary bypass (Fig. 6).

Adverse events

No serious adverse events occurred during the observation period (72 h after cardiopulmonary bypass). Patient 5 of

Table 3 Inotropic and vasodilating agents during postoperative care

Agents	iNO group (*n*)	Iloprost group (*n*)
Dobutamine	6	7
Epinephrine	5	8
Milrinone	3	4
Sodium nitroprusside	4	3

The figures represent the number of patients where the specific inotropic or vasodilating medication was used. Some patients needed more than one medication at the same time

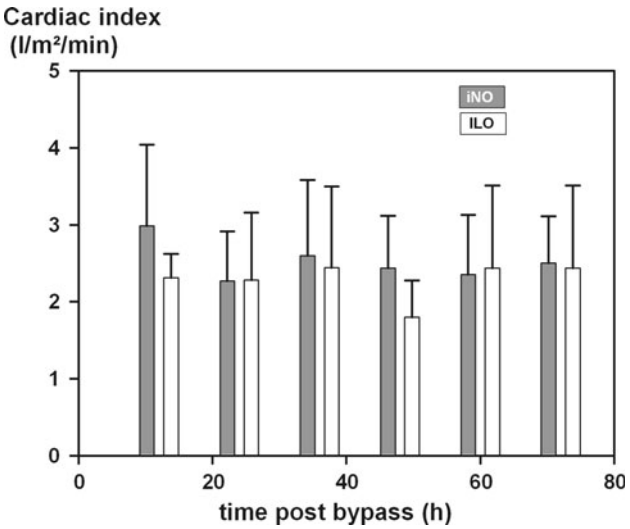

Fig. 3 Cardiac index measurements after intracardiac repair (mean [SD])

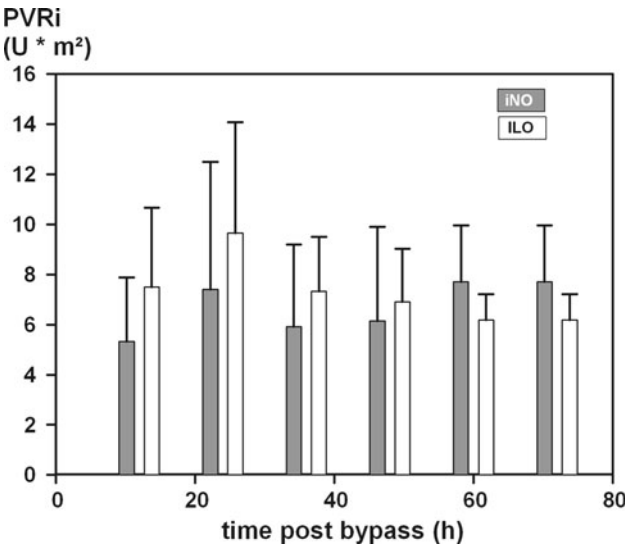

Fig. 4 Pulmonary vascular resistance index after intracardiac repair (mean [SD])

the iloprost group showed an increase in levels of C-reactive protein at 24 h after cardiopulmonary bypass. A bacterial infection was suspected and the patient was treated with antibiotics (cephalosporine plus flucloxacilline) for 7 days thereafter, but blood cultures remained sterile. Patient 8 of the iloprost group had thrombocytopenia count of <50 000 platelets/μl at day 2 after cardiopulmonary bypass, which was treated with thrombocyte concentrate and immunoglobulin. In both instances, there was probably no correlation with the study medication because inflammation and thrombocytopenia are the known complications after cardiopulmonary bypass. Bleeding complications were not observed in either the iNO or the iloprost group.

Mortality

No patient died during the observation period. Thereafter, there were three in-hospital deaths: in the iNO group, patient 6 died 14 days after surgery from chronic respiratory failure; in the iloprost group, patient 5 died 104 days after surgery from pneumonia and patient 6 died 125 days after surgery from chronic respiratory failure.

Discussion

This is the first pilot, open-label, randomized study to compare the effects of iNO and aerosolized iloprost in infants with a congenital heart defect, left-to-right shunt and severe pulmonary hypertension after intracardiac repair. Our inclusion criteria were chosen to select patients known to be at the highest risk for postoperative pulmonary hypertension. The high proportion of patients with trisomy 21 is explained by the fact that this population is known to be at high risk of postoperative pulmonary hypertension. In this pilot study, inhaled iloprost was equally effective on pulmonary hypertension as iNO reflected by frequency of PHTC and pulmonary arterial pressure. These preliminary results are in agreement with a previous observational open-label study of 12 children with PHTC after intracardiac repair, where iloprost was shown to be effective as an acute treatment [8].

A previous study in 15 children with congenital heart defects and left-to-right shunt analyzed the acute effects of iNO and iloprost as pulmonary vasodilating substances [9]. In the majority of patients published in the series of Rimensberger and co-workers 2001 [9], iNO and iloprost were used as substances to test acute pulmonary vasoreactivity before surgery, and in 5/15 patients only iNO and iloprost were used to test acute pulmonary vasoreactivity after intracardiac repair.

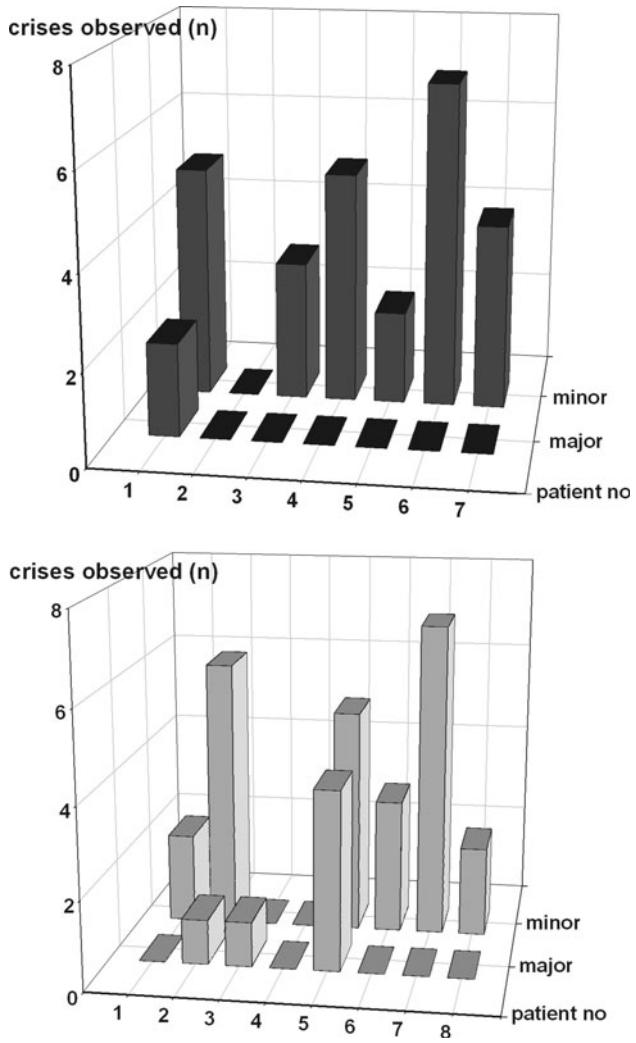

Fig. 5 Pulmonary hypertensive crises after intracardiac repair in patients treated with iNO (*black bars*) and in patients treated with iloprost (*gray bars*)

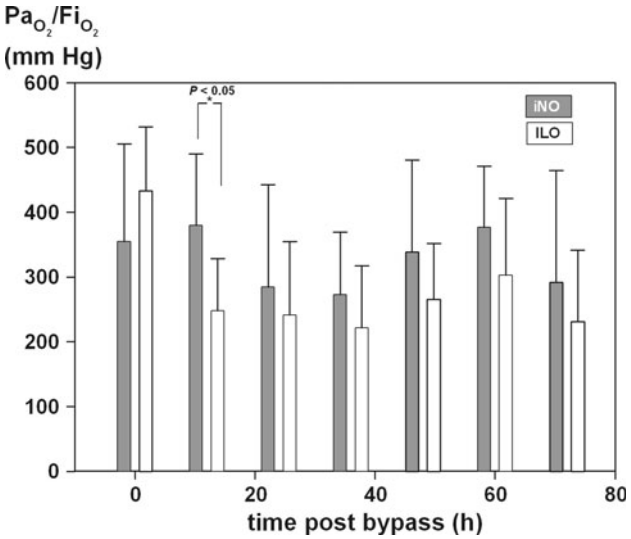

Fig. 6 The ratio of arterial oxygen tension to the fraction of inspired oxygen after intracardiac repair in patients treated with iNO (*dark grey bars*) and in patients treated with Iloprost (*open bars*)

At present, more data are available from studies using iNO to treat pulmonary hypertension after cardiopulmonary bypass: In a placebo-controlled study, Miller and co-workers [4] studied the effect of iNO at a concentration of 10 ppm and propagated the use of prophylactic iNO because iNO reduced the risk of PHTC after intracardiac repair, although it did not abolish the risk. Day and co-workers [5] used iNO at a concentration of 20 ppm in 20 patients, but were not able to show beneficial effects on pulmonary hemodynamics and gas exchange after operation for congenital heart disease. Previous studies with iNO have shown that low doses of iNO (e.g., 2 ppm) are as effective at lowering PAP as higher doses (10–20 ppm) [8]. We therefore used iNO at 10 ppm like other groups [14]. As in previous studies, the therapy with iNO did not entirely prevent PHTCs from occurring [5].

Iloprost has been used in children to test for acute pulmonary vasoreactivity [9, 15–17]. Recently, inhaled iloprost was used as a chronic treatment in 22 pediatric patients presenting with idiopathic pulmonary hypertension ($n = 12$) or associated with congenital heart disease ($n = 10$) [16]. In a majority of these patients, aerosolized iloprost was given in addition to various pulmonary hypertension-specific medications, such as bosentan, epoprostenol, sildenafil, or treprostinil. The response to iloprost was found to be equivalent to iNO in testing acute pulmonary vasoreactivity, and in many patients the transition from intravenous epoprostenol to inhaled iloprost was well tolerated.

Our study focused on patients with pulmonary hypertension immediately after intracardiac repair. Inhaled iloprost has been found occasionally to induce bronchoconstriction [16]. This explains for the much higher frequency of pulmonary hypertensive crises compared with the frequency reported by others for patients with left-to-right shunt in the postoperative period [2]. In our study, no such adverse reaction was observed; the difference may be well explained by the fact that our patients were intubated and ventilated mechanically.

The ratio of PaO_2 to FiO_2 tended to be lower in children treated with iloprost than in those with iNO in our study, but this was only significantly different at 12 h after weaning from cardiopulmonary bypass. The bronchodilating effect of iNO is weak in healthy humans, but may increase in several disease conditions [18]. As a limitation the small series presented did not allow for more detailed analysis. The effect of inhaled iloprost and iNO on the ratio of PaO_2 to FiO_2, therefore, should be studied in a larger

number of patients with special focus on ventilator parameters.

As a limitation of our study the interpretation of the difference between the number of PHTCs between the two groups may be explained: (1) by the small number of patients in this pilot study and/or; (2) by differences with respect to the cardiac anatomy and the complexity of the surgical treatment. This could explain that the patients in the iloprost group were mechanically ventilated longer and tended to need more inotropic agents compared to the patients in the iNO group.

The hospital mortality was 1/7 for iNO and 2/8 for iloprost group of patients. Given the small number of patients there was no statistical difference with respect to mortality for one of the treatment. Any deaths occurred well after the end of the observation period (i.e., >72 h after cardiopulmonary bypass) were due to known problems associated with severe postoperative pulmonary hypertension such as respiratory failure after long-standing mechanical ventilation.

A limitation of this study is that we could not determine lung function parameters in our ventilated patients. A further limitation is the small number of participants in both treatment groups, but our study is the largest published to date comparing the effects of iNO with iloprost.

In conclusion, this pilot study shows that aerosolized iloprost has a favorable safety profile. Our data show that neither iNO nor iloprost alone abolished the occurrence of major PHTCs in patients at high risk of severe postoperative pulmonary hypertension. Our data do not allow drawing conclusions on the efficacy of iNO compared to inhaled iloprost for the treatment of perioperative pulmonary hypertension in infants undergoing intracardiac repair with cardiopulmonary bypass. However, clearly, studies are needed to compare the efficacy of both substances in larger series of patients at risk for pulmonary hypertension after intracardiac repair. Moreover, studies analyzing the efficacy of a combination of the two vasodilatation agents are needed.

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References

1. Loukanov T, Arnold R, Gross J, Sebening C, Klimpel H, Eicjorn J, Hoss K, Ulmer HE, Kark M, Gorenflo M (2008) Endothelin-1 and asymmetric dimethylarginine in children with left-to-right shunt after intracardiac repair. Clin Res Cardiol 97(6):383–388
2. Lindberg L, Olsson AK, Jogi P, Jonmarker C (2002) How common is severe pulmonary hypertension after pediatric cardiac surgery? J Thorac Cardiovasc Surg 123:1155–1163
3. Bando K, Turrentine MW, Sharp TG, Sekine Y, Aufiero TX, Sun K, Sekine E, Brown JW (1996) Pulmonary hypertension after operations for congenital heart disease: analysis of risk factors and management. J Thorac Cardiovasc Surg 112(6):1600–7; 1607–9
4. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS (2001) Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study Lancet 357(9255):558–9
5. Day RW, Hawkins JA, McGough EC, Crezeé KL, Orsmond GS (2000) Randomized controlled study of inhaled nitric oxide after operation for congenital heart disease. Ann Thorac Surg 69(6):1907–1912
6. Bizzarro M, Gross I (2005) Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev 19:(4)
7. Macrae DJ, Field D, Mercier JC, Møller J, Stiris T, Biban P, Cornick P, Goldman A, Göthberg S, Gustafsson LE, Hammer J, Lönnqvist PA, Sanchez-Luna M, Sedin G, Subhedar N (2004) Inhaled nitric oxide therapy in neonates and children: reaching a European consensus. Intensive Care Med 30(3):372–380
8. Limsuwan A, Wanitkul S, Khosithset A, Attanavanich S, Samankatiwat P (2008) Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol 129(3):333–338
9. Rimensberger PC, Spahr-Schopfer I, Berner M, Jaeggi E, Kalangos A, Friedli B, Beghetti M (2001) Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation 103:544–548
10. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK (1987) Primary pulmonary hypertension: a nationwide prospective study. Ann Intern Med 107:216–223
11. Bando K, Vijayaraghavan P, Turrentine MW, Sharp TG, Ensing GJ, Sekine Y, Szekely L, Morelock RJ, Brown JW (1997) Dynamic changes of endothelin-1, nitric oxide, and cyclic GMP in patients with congenital heart disease. Circulation 96(9): 346–51
12. Pauli C, Fakler U, Genz T, Hennig M, Lorenz H-P, Hess J (2002) Cardiac output determination in children: equivalence of the transpulmonary thermodilution method to the direct FICK principle. Intensive Care Med 28:947–952
13. Vargo TA (1997) Cardiac catheterization: hemodynamic measurements. In: Garson A, Bricker Jt, Fisher DJ, Neish SR (eds) The science and practice of pediatric cardiology, 2nd edn. Williams&Wilkins, Baltimore, pp 961–993
14. Miller OI, Celermajer DS, Deanfield JE, Macrae DJ (1994) Very-low-dose inhaled nitric oxide: a selective pulmonary vasodilator after operations for congenital heart disease. J Thorac Cardiovasc Surg 108(3):487–494
15. Gorenflo M, Bettendorf M, Brockmeier K, Ulmer HE (2000) Pulmonary vasoreactivity and vasoactive mediators in children with pulmonary hypertension. Z Kardiol 89:1000–1008
16. Ivy DD, Doran AK, Smith KJ, Mallory GB Jr, Beghetti M, Barst RJ, Brady D, Law Y, Parker D, Claussen L, Abman SH (2008) Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 51(2):161–9
17. Limsuwan A, Khosithseth A, Wanichkul S, Khowsathit P (2009) Aerosolized iloprost for pulmonary vasoreactivity testing in children with long-standing pulmonary hypertension related to congenital heart disease. Catheter Cardiovasc Interv 73(1): 98–104
18. Högman M, Frostell CG, Hedenström H, Hedenstierna G (1993) Inhalation of nitric oxide modulates adult human bronchial tone. Am Rev Respir Dis 148(1):1474–1478