Effect of prostaglandin E1 inhalation on pulmonary hypertension following corrective surgery for congenital heart disease

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BACKGROUND: Intravenous infusion of prostaglandin E1 (PGE1) has been used to treat pulmonary arterial hypertension (PAH); however, the efficacy and safety of inhaled PGE1 is unclear.
OBJECTIVES: To investigate the effect of inhaled PGE1 on PAH following corrective surgery for congenital heart disease.
METHODS: Sixty patients with postoperative residual PAH following corrective surgery for congenital heart disease were randomly assigned to a control group, a PGE1 infusion group (intravenous PGE1 infusion; 30 ng/kg/min daily for 10 days) or a PGE1 inhalation group (100 µg nebulized PGE1 every 8 h for 10 days). Systolic blood pressure, mean pulmonary arterial pressure, arterial oxygen pressure, oxygen saturation and serum endothelin-1 level were measured before and after the treatment.
RESULTS: At the end of the study, the mean pulmonary arterial pressure in the two PGE1 groups were lower than in the control group (P<0.01), whereas the mean arterial oxygen pressure was higher (P<0.01). Compared with the PGE1 infusion group, the mean pulmonary arterial pressure in the PGE1 inhalation group was lower (P<0.01) whereas the arterial oxygen pressure was higher (P<0.01). The mean endothelin-1 levels in the two PGE1 groups were lower than in the control group (P<0.01), but there was no statistically significant difference in endothelin-1 levels between the PGE1 inhalation and infusion groups (P>0.05).
CONCLUSIONS: In pediatric patients with PAH, PGE1 inhalation was associated with a reduction in pulmonary arterial pressure and improvement in arterial blood oxygen levels.

Key Words: *Congenital heart disease; Postoperative; Prostaglandin E1; Pulmonary hypertension*

Pulmonary arterial hypertension (PAH) in patients with congenital heart disease is largely due to left-to-right shunt, which triggers a series of changes in the vascular structure and function of the pulmonary arteries (1). Correction of congenital heart disease and the closure of the left-to-right shunt are the best ways of preventing PAH; unfortunately, postoperative PAH, both in the immediate period after surgical repair and during long-term follow-up, is common (2). Postoperative PAH is associated with significant morbidity and mortality, and its management remains a significant challenge (1-4). Intravenous prostaglandin E1 (PGE1), a member of the prostanoid family, was found to reduce pulmonary pressure and improve clinical outcomes in a group of adult patients with PAH (5). Intermittent intravenous administration of PGE1 for up to 12 months has been found to lower mean pulmonary arterial pressure (MPAP) and improve five-year survival rates (6). Earlier studies have also found that inhalation of a prostanoid, such as iloprost, is associated with a reduction in the residual postoperative PAH and the right ventricular afterload following pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension (7). However, little is known about the effect of inhaled prostanoids on postoperative PAH in patients with congenital heart disease. The aim of the present study was to investigate the effect of inhaled PGE1 on the pulmonary pressure and arterial oxygen pressure in patients with PAH following corrective cardiac surgery.

METHODS

Patient selection

The present study was approved by the Human Research Ethics Committee of Liaocheng People's Hospital (Liaocheng, China). Informed written consent was obtained from all participants. Between January 2006 and October 2010, 276 pediatric patients (<18 years of age) who underwent corrective surgery were screened for inclusion in the present study, and 65 (23.4%) were found to have postoperative PAH on day 5 following surgery. Among the patients with postoperative PAH, 60 agreed to participate in the present study. The mean (± SD) age of the participants was 2.9±1.9 years (32 males, 28 females). The general characteristics of these patients are summarized in Table 1.

All patients exhibited clinical symptoms of pulmonary hypertension, which was confirmed by preoperative Doppler echocardiographic studies. Physical examination, echocardiography and blood oxygen assessments were performed on day 5 following surgery. PAH was defined as an increase in pulmonary arterial systolic pressure ≥50 mmHg and MPAP >25 mmHg at rest, in the absence of other causes of precapillary pulmonary hypertension such as pulmonary hypertension due to lung diseases or chronic thromboembolic pulmonary hypertension.

Transthoracic echocardiography

MPAP and ventricular function were evaluated using colour Doppler echocardiography (HP SONOS 5500, Philips, Netherlands) before the preoperative PGE1 treatment, on day 5 following the corrective surgery and at the end of the 10-day postoperative PGE1 treatment period. Pulmonary arterial systolic pressure was calculated from the tricuspid regurgitation velocity and pressure gradient, and the estimated right atrial pressure (8):

$$\text{Pulmonary arterial systolic pressure} = \text{tricuspid regurgitation pressure gradient} + \text{estimated right atrial pressure}$$

The MPAP was subsequently calculated according to the following formula (13):

$$\text{MPAP} = 0.61 \times \text{pulmonary arterial systolic pressure} + 2\ \text{mmHg}$$

Standard parasternal long-axis, short-axis, and apical four- and two-chamber views were obtained. The cardiologists who performed echocardiographic and New York Heart Association functional class assessments were blinded to the patients' group.

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TABLE 1
Baseline characteristics of the patients

Variable	Control	Administration of PGE1	
		Infusion	Inhalation
Age, years	2.9±1.9	2.7±2.3	3.6±1.9
Female sex, n (%)	7 (35)	8 (40)	13 (65)
Cardiac defects, n (%)			
VSD	12 (60)	13 (65)	14 (70)
ASD	3 (15)	2 (10)	3 (15)
VSD + ASD	3 (15)	4 (20)	2 (15)
VSD + PDA	2 (10)	1 (5)	0 (0)
ASD + PDA	0 (0)	0 (0)	1 (5)
Heart rate, beats/min	137±11	132.02±11.47	133.75±7.27
SBP, mmHg	98.21±5.49	96.40±6.29	98.64±6.21
Mean BP, mmHg	70.68±4.91	67.95±7.44	68.92±8.18
Mean PAP, mmHg	52.95±15.28	50.45±14.73	49.45±13.50
PO_2, mmHg	89.20±5.99	92.05±6.73	92.90±6.64
Oxygen saturation, %	97.31±0.84	98.60±0.94	98.50±1.15

Data presented as mean ± SD unless otherwise indicated; n=20 per group. ASD Atrial septal defect; BP Blood pressure; PAP Pulmonary arterial pressure; PDA Patent ductus arteriosis; PGE1 Prostaglandin E1; PO_2 Partial pressure of oxygen; SBP Systolic blood pressure; VSD Ventricular septal defect

TABLE 2
Effect of prostaglandin E1 (PGE1) inhalation on pulmonary hemodynamics

Variable	Control	Administration of PGE1		P
		Infusion	Inhalation	
Heart rate, beats/min	135.4±10.15	126.40±10.35	127.00±8.39	0.007
Systolic BP, mmHg	97.4±4.49	92.35±21.83	98.6±11.20	0.353
Mean BP, mmHg	68.53±3.89	66.93±8.07	68.83±8.88	0.736
Mean PAP, mmHg	51.65±14.90	31.15±5.00	22.00±2.90	<0.001
Arterial PO_2, mmHg	106.35±9.45	113.25±11.74	129.90±21.93	<0.001
Oxygen saturation, %	98.35±1.46	99.95±0.22	99.60±0.82	0.422

Data presented as mean ± SD unless otherwise indicated; n=20 per group. BP Blood pressure; PAP Pulmonary artery pressure; PO_2 Partial pressure of oxygen

Study protocol

Patients were randomly divided into three groups (control group, PGE1 infusion group and PGE1 inhalation group, respectively) by drawing a number from a container. Once the hemodynamic assessment, including echocardiography, was completed, all patients in the three groups were treated with oral captopril (0.3 mg/kg/day to 0.5 mg/kg/day) if this treatment had not already been initiated. In the PGE1 infusion group, PGE1 was administered intravenously at a daily dose of 30 ng/kg/min in the hospital ward, or at the hospital clinics if the patients were being discharged. Each course of this treatment lasted 10 days. In the PGE1 inhalation group, 100 µg of PGE1 was aerosolized in 20 mL of normal saline, and was inhaled over 30 min. This dosage was repeated every 8 h for 10 consecutive days on the ward, or at the hospital clinics following the surgery. Patients in the control group did not receive PGE1 treatment.

Heart rate, systemic blood pressure, arterial oxygen pressure and oxygen saturation rate were measured before the treatment and at the end of the 10-day postoperative therapies. Arterial blood gas was assessed while patients were being administered 4 L oxygen through a nasal prong before and after the treatment.

Measurement of endothelin-1

Fasting venous blood was drawn in the mornings after echocardiographic examination. Endothelin-1 levels were measured using a commercially available radioimmunoassay kit (Fangqi, China). The measurement range was 0 pg/mL to 80 pg/mL, with an intermeasurement variability of <7%. Endothelin-1 levels were measured before the PGE1 therapy and at the end of the 10-day PGE1 treatment period.

TABLE 3
Effect of prostaglandin E1 (PGE1) inhalation on endothelin-1 (pg/mL)

Variable	Control	Administration of PGE1	
		Infusion	Inhalation
Before	97.45±12.34	99.45±12.95	100.55±10.58
After	90.25±11.96*	75.20±9.88*†	73.55±5.91*†

*Data presented as mean ± SD; n=20 per group. *P<0.05 compared with baseline values within the same group; †P<0.01 compared with the control group*

Statistical analysis

ANOVAs were used for analysis of continuous variables. For categorical data, Fisher's exact test was used. All data are presented as mean ± SD; P<0.05 was considered to be statistically significant. All data were analyzed using SPSS version 13.0 (IBM Corporation, USA).

RESULTS

General findings

There were no statistically significant differences in age, baseline cardiac defects, systolic blood pressure, pulmonary arterial pressure or arterial oxygen pressure among the three groups (Table 1; P>0.05). Although the proportion of female patients in the PGE1 inhalation group appeared to be higher than the other two groups, this did not reach statistical significance (P=0.205). All patients were New York Heart Association functional class I or II. None of the patients were treated with diuretics or digitalis before or following the surgery. However, all patients were treated with oral captopril following the surgery.

Effect on systolic blood pressure and MPAP

The mean heart rate and MPAP in the two PGE1 groups were lower than in the control group at the end of the 10-day postoperative treatment period (Table 2; P<0.01). The mean arterial oxygen pressure in the two PGE1 groups was higher than in the control group (P<0.01) but there was no statistically significant difference in the oxygen saturation rate among the three groups (P>0.05). Compared with the PGE1 infusion group, the MPAP in the PGE1 inhalation group was lower (P<0.01), whereas the arterial oxygen pressure was higher (P<0.01). The mean systolic blood pressure in the PGE1 inhalation group was higher than in the PGE1 infusion group (P<0.01).

Effect on endothelin-1

As shown in Table 3, there was no statistically significant difference in endothelin-1 levels among the three groups before the PGE1 therapy (P>0.05). At the end of the therapy, a statistically significant reduction in endothelin-1 was found in the three groups (P<0.05). However, at the end of the treatment, the mean endothelin-1 levels in the two PGE1 groups were lower than in the control group (P<0.01). There was no statistically significant difference in the mean endothelin-1 levels between the PGE1 infusion and PGE1 inhalation groups (P>0.05).

Side effects

In the PGE1 infusion group, local venous irritation (pain and redness) at the injection site was observed in six patients (30%). Five patients in the PGE1 infusion group (25%) and one in the PGE1 inhalation group (5%) experienced nausea and vomiting that resolved within 48 h. Pulmonary edema occurred in five patients in the PGE1 infusion group (25%) but did not occur in the PGE1 inhalation or control groups.

DISCUSSION

The main findings of the present study are: inhaled PGE1 reduced MPAP and improved arterial blood oxygen levels following corrective

surgery for congenital heart disease; PGE1 inhalation appeared to be as effective as intravenous PGE1 on postoperative pulmonary hypertension, but did not cause the venous irritations that were complications of intravenous PGE1 infusion; and PGE1 inhalation was associated with a reduction in serum endothelin-1 levels. These results indicate that PGE1 inhalation may be a safe and effective treatment for postoperative pulmonary hypertension in patients with congenital heart disease.

PGE1 is a potent vasodilator in both pulmonary and systemic arteries (8). It has been used to treat postoperative PAH including PAH following mitral valve replacement or open-heart surgery in children (9-11). PGE1 infusion also improved ventricular function and survival in PAH secondary to advanced heart failure (12). Although continuous or intermittent intravenous PGE1 infusion improves exercise tolerance, enhances quality of life and reduces mortality in patients with postoperative PAH (5,6), it is also associated with adverse effects such as pain or inflammation at the venous infusion site (6). In the present study, 30% of the patients who received intravenous PGE1 infusion experienced local venous irritation. We also found that a greater proportion of patients who were treated with intravenous PGE1 experienced gastrointestinal symptoms compared with the PGE1 inhalation group.

One of the concerns regarding aerosol PGE1 administration in the past has been the potential incomplete absorption of the drug by the respiratory system, which may cause variations in therapeutic effects or side effects. In animal models of acute or chronic pulmonary hypertension, inhaled PGE1 increased ventricular contractility and reduced pulmonary arterial pressure (13,14). Inhalation of a single 25 µg dose of aerosolized iloprost, a prostanoid analogue, was associated with an enhanced cardiac index and reduced MPAP and pulmonary vascular resistance (7). In the present study, inhalation of 300 µg/day of PGE1 for 10 days following the surgery was associated with a reduction in pulmonary arterial pressure similar to that induced by intravenous PGE1 infusion. Compared with the control group, there was no statistically significant reduction in systolic blood pressure or mean blood pressure following PGE1 inhalation, but there was a greater reduction in the MPAP and increase in arterial oxygen pressure. These results suggest that PGE1 inhalation may be a safe and effective treatment for postoperative PAH.

It is worth noting that the MPAP in the PGE1 inhalation group was lower than in the PGE1 infusion group at the end of the present study. The reasons for the greater pulmonary pressure reduction following PGE1 inhalation are not entirely clear. Direct vasodilation of the pulmonary vasculature is the main mechanism of action of the anti-PAH effect of aerosol PGE1 (7,13,14). When PGE1 is intravenously administered, it is rapidly eliminated by the lungs, and the half-life of intravenous PGE1 can be as short as 42 s (15). The clearance of intravenous PGE1 is, therefore, closely related to respiratory function and pulmonary blood flow. Inhaled PGE1 acts mainly on the lungs, with little systemic spillover due to extensive pulmonary metabolism (16). This local and direct action on the pulmonary vasculature may explain the greater pulmonary arterial pressure reduction in the PGE1 inhalation.

Previous studies have shown that endothelin-1 is a potent vasoconstrictor that plays a critical role in the pathogenesis of pulmonary hypertension (17-20). Reduction in pulmonary hypertension following captopril treatment was accompanied by a reduction in plasma endothelin-1 (20). In the present study, there was a statistically significant reduction in endothelin-1 levels in the control and the two PGE1 groups following the treatment. However, a greater reduction of endothelin-1 was found in the two PGE1 groups, suggesting that endothelin-1 reduction may have contributed to the improved pulmonary hypertension control in the PGE1-treated patients.

The present study has several limitations. First, only a single dose of inhaled PGE1 was administered. Therefore, the dose-dependent effect of PGE1 inhalation and, indeed, the optimal dose of inhaled PGE1 for PAH control is unknown. Second, patients were only treated with inhaled PGE1 for 10 days. Whether a longer-term treatment with PGE1 inhalation may offer better PAH control has yet to be clarified.

CONCLUSIONS

The present randomized clinical study has demonstrated that in pediatric patients with postoperative PAH, PGE1 inhalation was associated with a reduction in the MPAP and an increase in the arterial oxygen pressure. There was also a reduction in serum endothelin-1 levels following the PGE1 treatment. PGE1 inhalation was not associated with venous irritations that were observed in intravenous PGE1 infusion. Therefore, inhaled PGE1 may be used as a treatment for postoperative pulmonary hypertension; however, long-term effect and the optimal dose of inhaled PGE1 require further investigation.

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