Combined effect of aerosolized iloprost and oxygen on assessment of pulmonary vasoreactivity in children with pulmonary hypertension

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ABSTRACT

Objective: The evaluation of pulmonary vascular reactivity plays a significant role in the management of patients with pulmonary hypertension. Inhaled nitric oxide in combination with oxygen (O_2) has become widely used as an agent for pulmonary vasodilator testing. However, inhaled nitric oxide is not available in many developing countries. Recently, aerosolized iloprost was suggested as an alternative to nitric oxide for this purpose. In the present study, aerosolized iloprost was used together with O_2 in the pulmonary vasoreactivity test of children with severe pulmonary hypertension. Thus, the synergistic effect of both vasodilators was utilized without extending the duration of cardiac catheterization.

Methods: The prospective cohort study registered a total of 16 children with severe pulmonary hypertension whose median age was 4.5 years. Hemodynamic parameters were quantified before and after the vasoreactivity test. Increased left-to-right shunt, pulmonary vascular resistance of <6 Woods units (WU)/m^2 and a pulmonary-systemic resistance ratio of <0.3, as well as a decrease >10% in the pulmonary vascular resistance and pulmonary-systemic vascular resistance ratio after the vasoreactivity test were accepted as a positive response. The data were analyzed using Wilcoxon signed-rank and the Mann-Whitney U tests.

Results: Eleven children gave a positive response to the vasoreactivity test, while 5 children did not respond. Pulmonary vascular resistance dropped from 9.98±1.39 WU/m^2 to 5.08±1.05 WU/m^2 (p=0.013) and the pulmonary-systemic vascular resistance ratio fell from 0.68±0.08 to 0.32±0.05 (p=0.003) in the children who were responsive. No side effects were observed related to iloprost administration.

Conclusion: Administration of inhaled iloprost in combination with O_2 for pulmonary vasoreactivity testing can be useful for correctly identifying pulmonary vasoreactivity without extending the duration of cardiac catheterization. *(Anadolu Kardiyol Derg 2014; 14: 383-8)*

Key words: pulmonary hypertension, iloprost, children

Introduction

The most common causes of pulmonary arterial hypertension (PAH) in children are PAH associated with idiopathic and congenital heart diseases. PAH is a major factor contributing to morbidity and mortality in children (1, 2). Determination of pulmonary vasoreactivity remains an important tool with which to evaluate the pulmonary vascular beds, as it enables the best treatment option and prognosis to be determined. All patients with a left-to-right shunt who have a pulmonary vascular resistance (PVR) >6 Woods units (WU) m^2 or a pulmonary-systemic resistance ratio (Rp/Rs) >0.3 should be given a vasoreactivity test. As far as patients with primary pulmonary hypertension are concerned, response to the pulmonary vasoreactivity test is a significant marker for survival and can identify patients who will benefit from chronic medical treatment. Therefore, the identification of pulmonary vascular reactivity is of critical importance in the management of patients with PAH (3-5).

Inhaled nitric oxide (iNO) in combination with inhaled oxygen (O_2) has become the standard in pulmonary vasoreactivity testing (6, 7). However, nitric oxide administration gives rise to the need for a delivery system, making the test more expensive and complicated. Thus, nitric oxide administration is not always possible in developing countries in particular. Furthermore, possibly life-threatening rebound phenomena have been described with iNO (8, 9). Therefore, effective, reliable a nd cost-effective alternatives are needed for use in the current pulmonary vasoreactivity tests (10, 11).

Iloprost, a stable prostacyclin analogue, has recently become a diagnostic tool comparable to iNO, thanks to its appropriate reliability profile, and is used in identifying the vasodilator

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capacity of the pulmonary bed in children with PAH. Since they exercise selective pulmonary vasodilation, aerosolized prostanoids have a smaller systemic hypotension-inducing effect, and they also possess advantages over parenteral prostacyclin analogues, whose administration requires a central catheter, which can bring about thrombotic or infectious complications (12, 13).

Breathing O_2 is one of the standard methods used for testing pulmonary vasodilation in the pediatric cardiac catheterization laboratory. It has the advantage of being readily available in all institutes and is easily administered. However, it was reported that O_2 by itself might prove insufficient in identifying some patients who actually had pulmonary vascularity (5, 7).

There are fewer studies concerning the use of aerosolized iloprost in pulmonary vasoreactivity tests in children (13, 14). It was reported that vasoreactivity testing with aerosolized iloprost may be of benefit preoperatively for identifying surgical candidates among children with PAH related congenital heart disease (15). But in these studies, iloprost was used alone for vasoreactiviy testing. To best of our knowledge, no study carried out using administration of inhaled iloprost in combination with O_2 for pulmonary vasoreactivity testing.

The present study aimed to evaluate the efficiency and reliability of using aerosolized iloprost in combination with O_2 in pulmonary vasoreactivity testing in children with severe pulmonary hypertension.

Methods

Study design

This prospective cohort study was conducted in the Department of Pediatric Cardiology of İnönü University Medical School between the years 2010 and 2012.

Study population

The study population consisted of a total of 16 children, of whom 15 had severe PAH secondary to congenital heart disease and one was diagnosed as having primary pulmonary hypertension. The diagnosis of PAH was established by cardiac catheterization. At catheterization, patients who were found to have either a PVR >6 WU. m^2 or an Rp/Rs >0.3 received aerosolized iloprost (Ilomedin®, Schering AG, Berlin, Germany).

Exclusion criteria were neonates, patients with diabetes mellitus, systemic hypertension, renal failure and anaemia, as well as patients who had undergone emergency catheterization.

The study protocol was approved by the institutional Ethics Committee and the parents of all the children were informed about the study, and their written consents were taken.

Study protocol

Haemodynamic monitoring

Cardiac catheterization was performed using Philips Integris H5000 equipment (Philips Medical Systems, Best, The Netherlands) in all children in order to obtain haemodynamic data and angiographic information. Local anaesthesia for femoral catheter insertion was achieved with lidocain. During cardiac catheterization, patients were sedated with midazolam (dormicum 0.1 mg/kg intravenously; maximum dose 15 mg). Appropriate-sized introducer sheaths were placed into both the femoral vein and artery. Intravascular pressures were measured concomitantly with fluid-filled transducers. Two transducers were positioned at the mid-axillary line and zeroed at atmospheric pressure. Systolic, diastolic, and mean pulmonary and systemic arterial pressures were monitored continuously, and right and left atrial pressures were determined at baseline and at the end of the drug-application period. In the absence of interatrial communication, pulmonary capillary wedge pressure was measured instead of left atrial pressure. If possible, baseline haemodynamic parameters were obtained while the children were breathing room air. Pulmonary and systemic blood-flow calculations, based on the Fick principle, were obtained from assumed O_2 consumption. Arterial blood gases were obtained for determination of dissolved oxygen. Systemic vascular resistance and PVR were calculated with standard formulas and indexed to body surface area. The pulmonary-to-systemic vascular resistance ratio (Rp/Rs) was then calculated. Heart rate, heart rhythm and transcutaneous arterial O_2 saturation were also continuously monitored.

Iloprost administration

Aerosolized iloprost was administered at a dose of 25 $ng/kg^{-1}/min^{-1}$ diluted in 1.5 mL of isotonic saline solution and nebulized for 10 minutes with 100% O_2 through a face mask to achieve alveolar deposition of the drug (16).

Following iloprost administration, a simultaneous decrease in both the PVR and Rp/Rs of >10% or a concomitant PVR of less than PVR 6 WU. m^2 or an Rp/Rs less than 0.3 was considered indicative of selective reactivity of the pulmonary vascular bed, and patients exhibiting responses of this magnitude were defined as responders (3, 6, 15).

Statistical analysis

Data was analysed using the SPSS 13.0 software package (SPSS Inc., Chicago, Illinois). Haemodynamic changes following iloprost administration were compared by means of the Wilcoxon signed-rank test. The Mann-Whitney U test was used to compare baseline age, PVR and Rp/Rs between iloprost responders and non-responders. The level of statistical significance was set at $p<0.05$.

Results

Demographic and clinical characteristics of the population

Of our cases, 12 (75%) were girls and 4 (25%) were boys. Their mean age was 5.06±3.88; the median age was 4.5 (1-16) years. The demographical and clinical properties of the patients are presented in Table 1.

Table 1. Demographical and clinical properties of the patients

Patient No.	Gender	Age	Diagnosis
1	F	1 y	PDA
2	F	3 y	Truncus arteriosus
3	F	7 y	PDA
4	F	4 y	Primary PH
5	F	7 y	VSD
6	F	5 y	PDA
7	M	8 y	VSD
8	F	1 y	AVSD+PDA
9	M	1 y	PDA
10	F	3 y	VSD
11	F	16 y	VSD+ASD+PDA
12	F	8 y	VSD
13	M	7 y	AVSD+Cor triatriatum
14	F	2 y	VSD+ASD
15	F	2 y	AVSD
16	M	6 y	VSD

ASD - atrial septal defect; AVSD - complete atrioventricular septal defect; F - female; M - male; PDA - patent ductus arteriosus; PH - pulmonary hypertension; VSD - ventricular septal defect; y - years

Haemodynamic evaluations

The mean±SEM PAP was 65±4.55 mm Hg, the mean±SEM PVR was 10.64±1.11 WU. m^2 and the mean±SEM Rp/Rs was 0.65±0.06 in all patients at baseline. An examination of the ages, mean PAP, PVR, Rp/Rs and Qp/Qs before the test showed that there was no statistically significant difference between the responder and non-responder groups (p>0.05).

Based on haemodynamic calculations, eleven children were evaluated to be responsive to iloprost, while the remaining five were non-responsive. In the responsive patients, the mean±SEM PVR fell from 9.98±1.39 WU.m^2 to 5.08±1.05 WU.m^2 (p=0.013), the mean±SEM Rp/Rs fell from 0.68±0.08 to 0.32±0.05 (p=0.003) and the mean±SEM PAP fell from 65±4.55 to 50.55±5.04 (p=0.028) (Table 2). The magnitude of iloprost-induced vasodilation varied among responders. There was no statistically significant change in the mean systemic arterial pressure and systemic resistance (p>0.05). Aerosolized iloprost also increased the left-to-right shunt (p<0.001) in responsive patients. Aerosolized iloprost was tolerated well. No side effects were observed during iloprost administration or within the 24 hours following inhalation in our study.

Individual changes in the PVR and Rp/Rs in response to iloprost in these cases are presented in Figures 1 and 2. Individual changes in the PVR and Rp/Rs with iloprost in the nonresponder group are presented in Figures 3 and 4.

Discussion

In the present study, aerosolized iloprost was used together with O_2 in the pulmonary vasoreactivity test of children with severe hypertension. Eleven children gave a positive response to the vasoreactivity test. Pulmonary vascular resistance and the pulmonary-systemic vascular resistance ratio fell significantly in the children who were responsive (p=0.013, p=0.003, respectively).

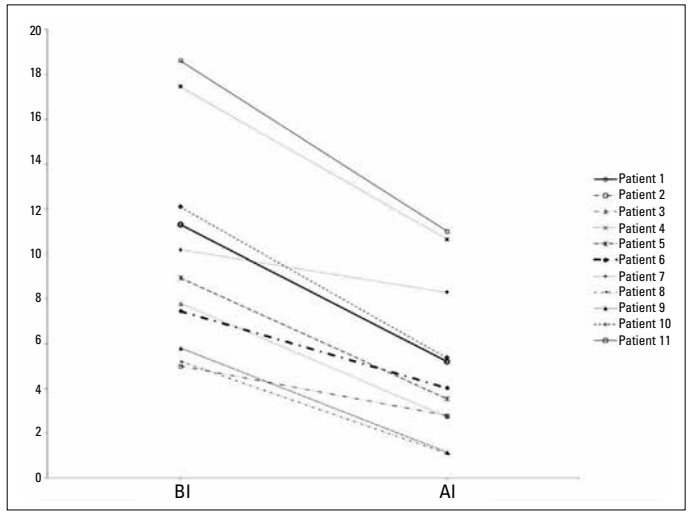

Figure 1. Individual changes in pulmonary vascular resistance observed in the responder group of 11 children before iloprost (BI) and after iloprost (AI)

Although most of the congenital cardiac defects that cause PAH can be corrected with surgery in childhood, the timing of surgery is of critical importance in these patients. Surgical correction in children who have irreversible pulmonary vasculopathy that has progressed secondary to congenital heart disease is counter-indicated, as it is associated with a high risk of morbidity and mortality. The pulmonary vasoreactivity test guides both the decision as to whether or not to carry out surgical reparation, and prognosis determination. A negative vasoreactivity test result confirms the diagnosis of a permanent vascular obstructive disease (3, 15). As far as children with primary pulmonary hypertension are concerned, the vasoreactivity test is the best treatment alternative and offers invaluable data regarding the prognosis (3, 4).

The present study employed aerosolized iloprost together with O_2 to identify pulmonary vasoreactivity in children with pulmonary hypertension and made use of the synergistic effect of both vasodilators without extending the duration of cardiac catheterization.

The fact that iNO administration in the pulmonary vasoreactivity test is relatively complicated and expensive has led to a search for different drugs that can be used for the same purpose (17). The need for more cost-effective, easily accessible and easily administered drugs that can drop pulmonary pressure selectively has become more acute, especially in centres where it is difficult to obtain iNO. Previous studies demonstrated that short-term aerosolized iloprost administration exercised positive effects on pulmonary haemodynamics without causing a significant decrease in systemic blood pressure in adults with primary pulmonary hypertension (18-20). In their study, Hallıoğlu

Table 2. Hemodynamic variables before and after vasoreactivity testing

	Responders (n=11)		Nonresponders (n=5)		
	Mean± SEM	**Median (Min-Max)**	**Mean± SEM**	**Median (Min-Max)**	**#*P* (R-NR)**
Age (y)	5.09±1.33	4 (1-16)	5±1.26	6 (2-8)	NS
PAP (mm Hg)					
Before iloprost	65±4.55	62 (44-88)	67.2±2.48	69 (61-74)	NS
After iloprost	50.55±5.04	47 (30-78)	70.4±2.58	69 (66-80)	NS
**P* (BI-AI)	0.028		NS		
PVR (WU.m^2)					
Before iloprost	9.98±1.39	8.94 (5-18.62)	12.10±1.88	11.96 (7.2-17.4)	NS
After iloprost	5.08±1.05$^{\alpha}$	4.03 (1.09-11.01)	12.03±1.80	11 (7.86-17.2)	0.015
**P* (BI-AI)	0.013		NS		
Rp/Rs					
Before iloprost	0.68±0.08	0.57 (0.34-1.1)	0.59±0.05	0.62 (0.4-0.71)	NS
After iloprost	0.32±0.05	0.26 (0.08-0.64)	0.52±0.06	0.53 (0.31-0.67)	0.054
**P* (BI-AI)	0.003		NS		
Ao (mm Hg)					
Before iloprost	70.45±4.31	74 (45-92)	72.8±3.98	67 (65-83)	NS
After iloprost	72.82±4.42	72 (55-97)	76.8±4.68	72 (69-95)	NS
**P* (BI-AI)	NS		NS		

Data are presented as mean±SEM and median (min-max)
*Wilcoxon signed-rank test; #Mann-Whitney U tests
AI - after iloprost; Ao - aortic blood pressure; BI - before iloprost; Max - maximum; Min - minimum; NR - nonresponders; PAP - pulmonary arterial pressure; PV - pulmonary vascular resistance; R - responders; Rp/Rs - pulmonary to systemic resistance ratio; WU - Wood units

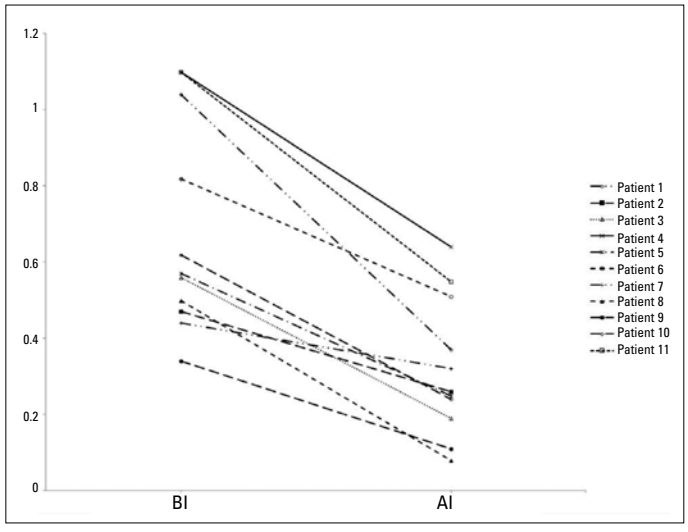

Figure 2. Individual changes in the pulmonary-to-systemic resistance ratio (Rp/Rs) observed in the responder group of 11 children before iloprost (BI) and after iloprost (AI)

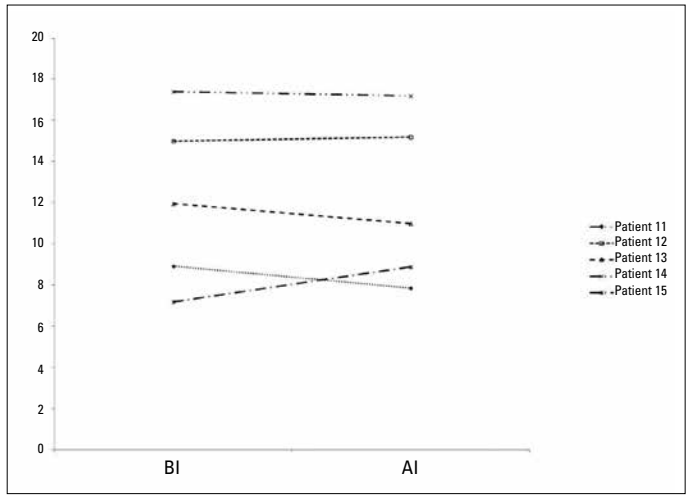

Figure 3. Individual changes in pulmonary vascular resistance observed in the non-responder group of 5 children before iloprost (BI) and after iloprost (AI)

et al. (21) compared the efficacy of the short-term administration of aerosolized and intravenous iloprost on pulmonary haemodynamics in children with pulmonary hypertension and found that aerosolized iloprost caused a significant decrease in the Rp/Rs ratio; however, intravenous infusion did not lead to a marked decrease in this ratio. Similarly, it was shown that aerosolized iloprost was as effective as iNO in selectively decreasing vascular pressure in the pulmonary vasoreactivity test. Hoeper et al. (18) reported that aerosolized iloprost throughout the duration of the acute test was a more potent pulmonary vasodilator than iNO in adults who had primary pulmonary hypertension. It was established in that study that aerosolized iloprost was tolerated well and did not produce any major side effects (18). Likewise, Zhang et al. (22) found that aerosolized iloprost had potent and selective pulmonary haemodynamic effects and was well tolerated in 212 adult patients with pulmonary hypertension.

There are fewer studies and data concerning the use of aerosolized iloprost in pulmonary vasoreactivity tests for children than for adults (10, 13, 14). In one of these studies,

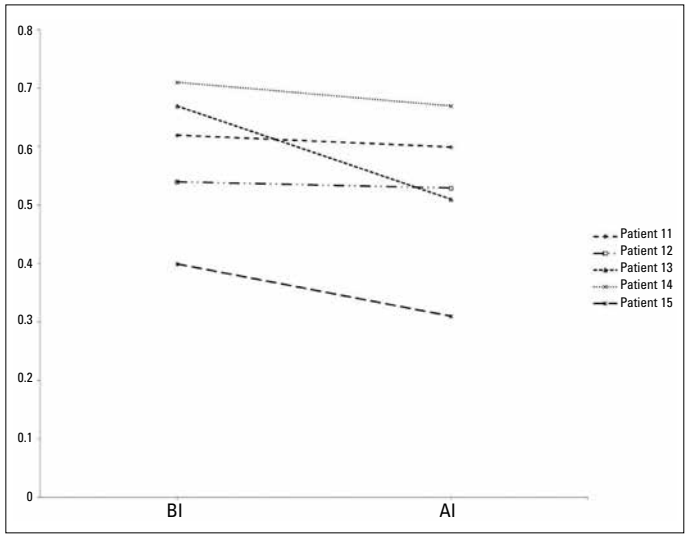

Figure 4. Individual changes in the pulmonary-to-systemic resistance ratio (Rp/Rs) observed in the non-responder group of 5 children before iloprost (BI) and after iloprost (AI)

Rimensberger et al. (10) found that iNO and aerosolized iloprost were equally effective in selectively reducing the pulmonary artery pressure, but that the combination of these two drugs did not provide any additional benefit in terms of decreasing pulmonary resistance. In another study, it was demonstrated that iNO and aerosolized iloprost had equal efficiency in selectively reducing the PVR in 15 children who had pulmonary hypertension secondary to congenital heart disease, and it was concluded that aerosolized iloprost could be an alternative to iNO in the pulmonary vasoreactivity test (10).

Similar to previous studies, this study has found that aerosolized iloprost reduced the PVR and the Rp/Rs ratio without causing any change in systemic arterial pressure or systemic vascular resistance. Administration of iloprost was generally well tolerated. None of the patients suffered any side effects for the 24 hours during and after the inhalation in our study.

Breathing O_2 is among the standard methods used for pulmonary vasodilator testing in the paediatric cardiac catheterization laboratory. However, it was reported that O_2 alone sometimes fell short in identifying some patients who actually had reactive pulmonary vascularity (5, 23). Limsuvan et al. (15), on the contrary, noted that two patients who were unresponsive to the vasoreactivity test using iloprost responded to the hyperoxia test and that there was also one patient who was a borderline non-responder, and successful corrective operations were conducted on all three of these patients. Therefore, they suggested that the use of iloprost as the single pulmonary vasodilator could prove inadequate in some patients, and hyperoxia testing should also be conducted in non-responders. It was noted in the same study that the hyperoxia test could prolong catheterization.

It was reported in another study that use of iNO together with O_2 caused additional pulmonary vasodilation on the reactive pulmonary vascular bed and that the combination could contribute to the identification of patients who could not be identified with O_2 or iNO alone (7). Since the pulmonary vasodilation mechanisms in all patients with PAH may not be the same, some patients may respond to one agent, while others may respond to another. There is no predictor that can be used to anticipate whether a patient with PAH will respond to a vasoreactivity test using iloprost. In our study, there was no difference between the ages, baseline haemodynamic parameters, and especially the PVR, Rp/Rs and Qp/Qs values of responders and non-responders. Thus, administration of the inhaled pharmacological agent together with O_2 in the vasoreactivity test may increase the rate of vasoreactivity without protracting catheterization. In our study, we postulated that combination testing with iloprost and O_2 may be provide additional pulmonary vasodilatation. Rather than carrying out individual pulmonary vasoreactivity tests with O_2 and iloprost and then comparing the two, we used both vasodilators in combination to increase the rate of vasoreactivity and to cut down the duration of catheterization.

Study limitations

Although the low number of patients is a limitation in our study, our patient population is representative of the typical patients who need vasoreactivity testing.

Conclusion

Our results suggest that iloprost in combination with O_2 may be used as the alternative choice in pulmonary vasoreactivity testing. Keeping the length of cardiac catheterization as short as possible, minimizing blood draw and reducing the test cost are the major considerations in pulmonary reactivity tests. Therefore, we think that the information we present in this study may be of benefit in this area. However this is the first study on efficacy and safety of aerosolized iloprost together with O_2 to identify pulmonary vasoreactivity, we are of the opinion that further studies with larger case series may provide illuminating data in this area.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - Ö.E., C.K., G.K.; Design - Ö.E., C.K., G.K.; Supervision - Ö.E., C.K., G.K.; Resource - Ö.E., C.K., G.K.; Materials - Ö.E., C.K., G.K.; Data collection&/or processing - Ö.E., C.K., G.K.; Analysis &/or interpretation - Ö.E., C.K., G.K.; Literature search - Ö.E., C.K.; Writing - Ö.E., C.K.; Critical reviews - Ö.E., C.K., G.K.

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