Original Article

Validity of Sildenafil Test in Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease According to Clinical and Echocardiographic Parameters

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Abstract

Background: *Pulmonary arterial hypertension is a complication of most congenital heart diseases. We sought to assess the effect of sildenafil on patients suffering from pulmonary arterial hypertension in association with congenital heart disease on the basis of clinical and echocardiographic parameters and compare the catheterization and treatment results so as to evaluate the predictive value of sildenafil on the operability of patients.*

Methods: *After primary echocardiography, 21 patients were selected for the final study with a diagnosis of moderate-to-large ventricular septal defect and pulmonary artery hypertension. They were divided into 3 age groups: younger than one year, 1 to 2 years, and older than 2 years. Before and one hour after the consumption of sildenafil, the patients had their oxygen saturation and blood pressure measured. Additionally, the patients underwent echocardiography and cardiac catheterization. The patients' operability was determined on the basis of their clinical condition and their response to oxygen inhalation in the catheterization room. Finally, the results of the drug response and final treatment were analyzed statistically.*

Results: *The 21 patients, who had ventricular septal defect and pulmonary arterial hypertension, were comprised of 8 (38%) boys and 13 (62%) girls. The patients aged from 2.5 to 204 months (mean 30 months). It was clear that the younger patients had a more positive response to the drug. All the patients who had a positive response to the drug were considered operable after catheterization and all of them had a positive response to treatment. There was no significant correlation between operable/inoperable conditions and response to treatment (P value=0.262), while there was a very significant correlation between response to treatment and response to drug (P value=0.005).*

Conclusion: *According to the results of this study and given the low cost and availability of sildenafil and its oral consumability on the one hand and the availability and non-invasiveness of echocardiography on the other, it seems that sildenafil is useful in determining the pulmonary vascular bed reactivity via echocardiographic parameters and facilitating the decision-making process for surgery in patients with pulmonary arterial hypertension and congenital heart diseases.*

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Introduction

Pulmonary arterial hypertension is an accompanying complication in most cases of congenital heart diseases. The state and reactivity of the pulmonary vascular bed are the main determinants of clinical manifestations, course of the disease, and feasibility of intervention and surgery.[1-3] The reactivity of the pulmonary vascular bed is usually assessed in these patients by oxygen at catheterization, but no response to oxygen is seen in some patients with a reactive pulmonary vascular bed.[3,4] Endogenous nitric oxide, an endothelial-cell-derived relaxing factor that has relaxing effects on the vascular bed, induces such effects by cyclic guanosine 3-5 mono phosphate, activation of protein kinase, and the channels of calcium and potassium.[3,5]

It has been shown in clinical studies that inhaled nitric oxide is the elective vasodilator of the pulmonary vascular bed.[6] Also, a low dosage of nitric oxide in association with oxygen has been used in the evaluation of the reactivity of the pulmonary vascular bed.[3,4]

Nonetheless, not only does nitric oxide inhalation require a complex ventilation system and monitoring but it is also costly and not readily available in developing countries.

The inhibitors of phosphodiesterase type 5, such as sildenafil, have been demonstrated to be able to dilate the pulmonary arteries by increasing the level of cyclic guanosine mono phopsphate.[2,7] In addition, several studies have demonstrated that sildenafil can improve clinical condition, exercise tolerance, and hemodynamic state in patients suffering pulmonary arterial hypertension.[8-10] Sildenafil is also believed to be effective in controlling pulmonary arterial hypertension in children in intensive care units as well as in those after surgery.[11]

The present study aimed to assess the effect of sildenafil on patients suffering from pulmonary arterial hypertension in association with left-to-right shunt in congenital heart diseases according to the parameters of echocardiography and compare the catheterization and treatment results in order to evaluate the predictive effect of sildenafil in the operability of patients. It is noteworthy that the effect of sildenafil on patients suffering from pulmonary arterial hypertension on the basis of echocardiographic parameters has never been studied in Iran.

Methods

This descriptive case series study was conducted on patients hospitalized in the pediatric ward of Shaheed Rajaei Cardiovascular Medical and Research Center with a primary diagnosis of congenital heart diseases and pulmonary arterial hypertension. Initially, 35 patients with the above-mentioned condition were selected. Pulse oxymetry and measurement of systolic and diastolic blood pressures of all these patients were done through their right arms. Additionally, the patients underwent transthoracic echocardiography using General electric Vivid 3 machine and were assessed again one hour after taking a single dose of sildenafil in tablet form by the dosage of 1mg/kg. The results of the clinical and echocardiographic assessments were registered. Table 1 depicts the assessed parameters.

Of the total 35 patients, 14 patients were excluded, with the reason being large patent arterial duct in 2 patients, primary pulmonary hypertension in 3, complete atrioventricular septal defect in 4, interrupted aortic arch in 1, aortico-pulmonary window in 1, subvalvular pulmonary stenosis in 1, previous surgical pulmonary artery banding in 1, and normal pulmonary artery pressure at echocardiography in 1. Finally, 21 patients whose major structural defects were large ventricular septal defect and had pulmonary arterial hypertension according to echocardiography were selected for the final study.

Table 1. The assessed parameters in clinical and echocardiographic aspects in terms of the number of patients

Number of patients assessed	parameters
O_2 sat	21
BP-sys	21
BP- Dias	21
TR	21
early PR	21
late PR	17
PAF-PG	18
QP/QS	20
VSD-PG	3

O_2 sat, O_2 Saturation by pulse oxymetry; BP-sys, Systolic blood pressure (mmHg); BP-dias, Diastolic blood pressure (mmHg); TR, Tricuspid regurgitation pressure gradient (mmHg); PR, Pulmonary regurgitation pressure gradient (mmHg); PAF-PG, Pulmonary valve flow pressure gradient (mmHg); QP/QS, Pulmonary blood flow to systemic blood flow ratio; VSD-PG, Ventricular septal defect flow pressure gradient (mmHg)

The clinical effects of the drug were determined by the changes in the patients' blood pressure and oxygen saturation according to pulse oximetry. Drug response was determined as follows according to the changes in the clinical and echocardiographic parameters: increase in oxygen saturation of at least 5 units or more; decrease of at least 10 mmHg in the regurgitant flow pressure gradient across the pulmonary and tricuspid valves; increase of at least 10 mmHg in the blood flow pressure gradient through the pulmonary valve and ventricular septal defect; and increase in pulmonary blood flow to systemic blood flow ratio of at least one unit.

A change in 4 or more parameters was a positive response, a change in 2 or 3 of the parameters was a relative response; and if one or none of the parameters changed, it was a negative response to the drug.

Of the 21 patients, 20 underwent catheterization and angiography. For one of the patients (2.5 months old) with a diagnosis of large ventricular septal defect and pulmonary arterial hypertension, angiography was not performed

because of the clinical condition.

During angiography, the patients underwent a hyperoxia test; and according to their responses to oxygen and their clinical conditions, they were categorized as operable or inoperable. For the operable patients, palliative (pulmonary artery banding because of multiple ventricular septal defects) or curative (ventricular septal defect closure) surgery was done.

At 6 months' follow-up, the patients were assessed via echocardiography. In the patients who had undergone pulmonary artery banding surgery, the blood flow pressure gradient across the pulmonary artery band was measured. If the peak pressure gradient was more than 40 mmHg and its mean was more than 20 mmHg associated with a reduction of more than 50% of the internal diameter of the pulmonary artery anatomically, the response to treatment was considered positive.

In the patients who had undergone curative surgery, the pressure gradient of the regurgitant flow across the pulmonary and tricuspid valves was measured. If the calculated pressure of the pulmonary artery and right ventricle was within the normal range, the response to treatment was regarded as positive.

The effects of drug consumption in both clinical and echocardiographic assessments were compared with the results of catheterization and finally with the results of treatment in the surgical method.

Data analysis was carried out with the aid of appropriate tests, including the paired t-test, Chi–square test, Kruskal-Wallis test, and Man-Whitney test, using SPSS 15.0 statistical analysis software.

Anywhere in this paper, the word "treatment" denotes surgical treatment and "medical treatment" means non-surgical management.

Results

The 21 patients with ventricular septal defect and pulmonary arterial hypertension were comprised of 8 (38%) boys and 13 (62%) girls. The patients aged from 2.5 to 204 months (mean 30 months). They were divided into 3 age groups: younger than one year, 1 to 2 years, and older than 2 years.

According to the assessed clinical and echocardiographic parameters, increase in oxygen saturation, decrease in the pulmonary regurgitant flow pressure gradient, increase in pulmonary blood flow to systemic blood flow ratio, and increase in the pulmonary artery blood flow in response to the drug were statistically significant (P value<0.05) (Table 2).

Ten (47.6%) patients had a positive response, 8 (38.1%) had a relative response, and 3 (14.3%) had a negative response to the drug (Table 3).

The amount of positive and relative response in the patients under 1 year was 100%, in patients between 1 and 2 years was 75%, and in patients above 2 years was 67% (Table 4).

Table 2. Changes in the clinical and echocardiographic parameters in response to sildenafil

Parameters (n)	Before drug*	After drug*	P value
O_2 sat (21) (%)	91.00±6.48	93.00±4.45	0.014
Bp-sys (21) (mmHg)	90.00±9.48	82.85±12.50	0.001
Bp-dias (21) (mmHg)	55.47±13.59	47.85±19.07	0.131
TR (18) (mmHg)	52.38±28.70	47.66±25.12	0.391
Early PR (21) (mmHg)	55.04±12.76	35.57±17.41	<0.001
Late PR (17) (mmHg)	33.00±10.18	20.64±14.47	<0.001
QP/QS (20)	2.45±1.34	3.17±1.52	<0.001
VSD-PG (3) (mmHg)	27.33±11.67	32.00±19.28	0.541
PAF-PG (18) (mmHg)	18.16±12.67	24.38±14.70	0.014

*Data are presented as mean±SD

O_2 sat, O_2 Saturation by pulse oxymetry; Bp-sys, Systolic blood pressure; Bp-dias, Diastolic blood pressure; TR, Tricuspid regurgitant flow pressure gradient; Early PR, Pulmonary regurgitant flow pressure gradient at initiation; Late PR, Pulmonary regurgitant pressure gradient at the end; QP/QS, Pulmonary blood flow to systemic blood flow ratio; VSD-PG Ventricular septal defect flow pressure gradient; PAF-PG, Pulmonary valve flow pressure gradient

Table 3. The drug response in all patients

Response	Frequency	Valid percent
Yes	10	47.6
Partial	8	38.1
No	3	14.3
TOTAL	21	100

Table 4. The drug response according to age groups*

AGE Group	Drug Response			
	Yes	Partial	No	Total
<1 y	6 (54.5)	5 (45.5)	0	11 (100)
1-2 y	1 (25)	2 (50)	1 (25)	4 (100)
>2 y	3 (50)	1 (16.7)	2 (33.3)	6 (100)
Total	10 (47.6)	8 (38.1)	3 (14.3)	21 (100)

*Numbers in the parenthesis are the related percentages

The reduction in the systolic blood pressure in response to the drug was statistically significant (P value≤0.001) (Table 2).

Seventeen of the 20 patients who were catheterized were considered operable and the remaining 3 patients were regarded as inoperable.

In one 2.5-month-old patient, the clinical condition, and not catheterization, determined the operability of the patient. Finally, of the 21 patients, 17 (81%) patients were treated surgically and 4 (19%) were treated by medical management.

All the patients who had a positive response to the drug were considered operable after catheterization and all of them had a positive response to treatment. One of the patients who did not respond to the drug and was considered operable (Table 5) died 4 days after ventricular septal defect repair

surgery because of right heart failure.

Of the 8 patients who had a relative response, 7 patients were deemed operable (Table 5). One of them died in ICU one day after pulmonary artery banding surgery because of bradycardia. Another patient died 3 months after ventricular septal defect closure surgery as a result of right heart failure and arrhythmia.

Table 5. The correlation of patients' condition and drug response*

Condition	Drug response			
	Yes	Partial	No	Total
Operable	10	7	1	18
	(55.6)	(5.6)	(38.9)	(100)
Inoperable	0	1	2	3
		(33.3)	(66.7)	(100)
Total	10	8	3	21
	(47.6)	(38.1)	(14.3)	(100)

*Numbers in the parenthesis are the related percentages

Four patients who just underwent medical management did not return to the clinic again after discharge during the study period.

It was clear in the statistical analysis that there was no significant correlation between operable/inoperable conditions and response to drug (P value=0.412). Furthermore, there was no significant correlation between operable/inoperable conditions and response to treatment (P value=0.262), while there was a very significant correlation between response to treatment and response to drug (P value=0.005).

Discussion

Pulmonary arterial hypertension secondary to congenital heart diseases is one of the main challenges in pediatric cardiology, especially when the patient is at borderline with respect to pulmonary artery pressure and pulmonary vascular obstructive disease. The determination of the pulmonary vascular bed reactivity to vasodilator agents is an important factor in the decision-making for surgery.[1]

In this study, the patients' response to sildenafil was positive in that we witnessed an increase in arterial blood O_2 saturation, decrease in the pressure gradient of the retrograde blood flow from the pulmonary and tricuspid valves, and increase the pulmonary blood flow to the systemic blood flow ratio, all of which account for the decrease in the pulmonary arterial blood pressure and increase in the pulmonary blood flow. These findings are compatible with those in the studies by Raja et al.,[9] Daga et al. (Daga SR, Valve C, jauvale S, Chagan MNM. Sildenafil for pulmonary hypertension associated with congenital heart defect. The Internet Journal of Pediatrics and Neonatology 2007;7-2.), Peiravian et al.,[11] and Sudhakaran et al (Sudhakaran S, Bogovic A, carberry J. Sildenafil for the treatment of pulmonary hypertension in children. Never too young for Viagra. RCH 2007.).

In this study, sildenafil caused a significant decrease in the systolic blood pressure, which is why these patients probably needed less amounts of the drug. In the Liki et al. study,[10] there were positive results even with lower dosages of drugs. As was expected, response to drug was better in young patients, especially in those less than 1 year.

A finding of great importance in the present study was that no significant correlation was found between the patients' condition and response to treatment, while there was a significant correlation between the patients' response to treatment and response to drug. As was mentioned before, the patients' operability or inoperability was determined via their clinical manifestations and their responses to the hyperoxya test at catheterization. It can, therefore, be concluded that sildenafil in comparison with oxygen can reliably predict the feasibility of surgery and its result in patients with pulmonary arterial hypertension. This finding chimes in with the results of the A'jami and et al. study.[3]

Conclusion

The results of the present study demonstrate that the patients who had a better response to treatment had a more positive response to the drug.

The low cost and availability of sildenafil and its oral consumability on the one hand and the availability and non-invasiveness of echocardiography on the other hand render sildenafil useful in determining the pulmonary vascular bed reactivity via echocardiographic parameters and facilitate the decision-making process for surgery in patients with pulmonary arterial hypertension and congenital heart diseases.

Further long-term studies with larger sample populations are, however, required to bolster the results of the present study.

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