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Protective effect of sildenafil in pulmonary hypertensive child with congenital heart disease

Adnan Khtan,[a] and Yasmeen Ali Hussien[b*]

[a]Department of Pediatric Cardiology, Ministry of Health, Maternity and Pediatric Hospital, Hilla, Iraq.
[b]Faculty of Pharmacy, Alkafeel University, Najaf, Iraq.
*Correspondence to Yasmeen Ali Hussien (email: yas.ali50@yahoo.com).
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Objective Pulmonary hypertension has been described as an elevation in mean pulmonary artery pressure (PAP) >25 mmHg at rest or 30 mmHg during exercise, which can be classified into primary and secondary pulmonary hypertension.
Methods In this study, subjects were divided into two groups of patients and controls. The patients were treated with Sildenafil for 3 months, starting with 0.2 mg/kg/dose, six times daily and then the dose was increased with an increment of 0.2 mg/kg/dose every 15 days. Echocardiography examination, including pulmonary artery pressure, tricuspid regurgitation velocity, and pulmonary artery acceleration time, as well as oxygen saturation (SpO_2) rate were measured every 15 days.
Results The results revealed that a significant decrease ($P < 0.05$) in the pulmonary artery and tricuspid pressure, and a significant increase ($P < 0.05$) in the rate of blood oxygen saturation and pulmonary artery acceleration time have been found.
Conclusion The results of this study reveal that Sildenafil has a great effect in the treatment of the secondary type of pulmonary hypertension and has a negligible effect on primary pulmonary hypertension.
Keywords sildenafil, pulmonary hypertensive child

Introduction

Pulmonary hypertension has been determined as an increase in mean pulmonary artery pressure (PAP) ≥25 mmHg at rest, or 30 mmHg during exercise, which can be classified into primary and secondary pulmonary hypertension.[1]

The main causes of pulmonary arterial hypertension (PAH), are low endothelial nitric oxide (NO) production, elevated phosphodiesterase type 5 (PDE5) expression and increased function of right ventricular myocardium and pulmonary artery smooth-muscle cells.[2] The main sign and symptoms in patients with pulmonary hypertension, include high tricuspid regurgitation (TR), jugular venous pressure, peripheral edema,[3] dyspnea, exercise intolerance, fatigue and decreased appetite.[4]

Phosphodiesterase type 5 inhibitors impede the degradation of cGMP and may potentiate pulmonary vasodilation with inhaled NO. Sildenafil is an oral PDE5 inhibitor that has been proven safe and effective for erectile dysfunction. Sildenafil was approved for the treatment of PAH by the Food and Drug Administration and by the European Medicines Agency in 2005. Some of the Sildenafil's beneficial effects may be exerted by inhibition of PDE1 and increase in antiproliferative effects of cyclic adenosine monophosphate (cAMP).[5] The treatment for PAH includes vasorelaxation, inhibiting cellular proliferation, and promoting apoptosis within the pulmonary artery wall. Moreover, as PAH is accompanied by right heart failure, another objective of treatment, as in subjects with left ventricular failure, is to elevate cardiac output by lowering afterload (pulmonary vascular resistance) and elevating ventricular inotropy. The ideal treatments for PAH is to lower pulmonary vascular resistance, increase the systemic circulation, and elevate right ventricular inotropy.[6] Therefore, the aim of this study was to examine the protective effect of Sildenafil in pulmonary hypertensive child with congenital heart disease.

Patients and Methods

Patients and Controls

A total of 43 pulmonary hypertensive patients (23 males and 20 females) were participating in this study, their mean ages were 7.322 ± 12.265 months, while the control represents the patients who were not treated by Sildenafil, and included eight cases (4 females and 4 males), with mean ages of 22.14 ± 22.157 months. Effect of Sildenafil on oxygen saturation (SpO_2) rate and PAP, TR, pulmonary artery acceleration time were considered in patients and controls.

Study Design

In this study, we have two groups of patients and controls. The patients were treated with Sildenafil for 3 months, starting with 0.2 mg/kg/dose six times daily and then the dose was increased to 0.2 mg/kg/dose every 15 days. Echocardiography examination, including PAP, TR velocity, PAAT, as well as oxygen saturation (SpO_2) rate were measured every 15 days.

Methods

Blood Sample Collection

Blood (3 ml) was drawn *in situ,* using a disposable 3 ml syringe, while a tourniquet was applied directly on the skin around the arm. The skin over the vein was sterilized with 70% ethyl alcohol, and then collected blood was poured into the EDTA tube, labeled with the patients' name and date of sampling. The blood was collected for hematological analysis.

Hematological Analysis

Determination of Packed Cell Volume

Anticoagulated whole blood was centrifuged and the volume occupied by the erythrocytes is expressed as a percentage of the total volume of packed cell volume (PCV).[7]

Examination of Blood Smear

Blood samples were processed as rapidly as possible after collection, the two types of blood sample are venous (anticoagulated) and capillary, as withdrawn by skin puncture (without anticoagulation). It includes state-of-the-art techniques, the results obtained from blood films are often definitive in a clinical situation.[8]

Detection of Oxygen Saturation (SpO_2)

A well-perfused finger that best fits in the sensor was chosen. Nail polish or artificial fingernail was removed. The finger was inserted into the finger sensor until the finger touches the finger stop. The sensor was positioned so that the cable rests along the palm of the hand. The connector was held rather than the cable, when connecting or disconnecting the finger sensor to the oximeter.[9]

Echocardiographic Examination

The PAP was considered as normal between 20 and 25 mmHg, in mild pulmonary hypertension was between 25 and 40 mmHg, in moderate pulmonary hypertension between 40 and 60 mmHg and in severe pulmonary hypertension above 60 mmHg, which was assessed by Doppler echocardiography, using three methods which allows assessment of PAP as follows:

Measurement of Tricuspid Regurgitation Velocity

This technique was supplemented by assessment of right ventricular (RV) pressure of TR jet.

Pulmonary artery pressure = RV systolic pressure = 4 (peak velocity)^2 + Right arterial (RA) pressure (RA pressure normal value = 8–10 mmHg).

The peak systolic *trans* tricuspid pressure gradient from the RV to the right atrium (RA) is represented by 4× (peak TR velocity)^2, therefore, systolic RV pressure is estimated by adding RA pressure to the pressure gradient, derived from TR velocity.

Peak Systolic Gradient Between the Right Ventricles (RV) and Left Ventricles (LV)

Is calculated, using the modified Bernoulli equation:

Right ventricular systemic pressure = Systemic blood pressure – 4(V)^2

Pulmonary Artery Acceleration Time

Acceleration time is the time interval between the beginning of the flow and its peak velocity, normal ≥120 ms, mild between 80 and 120 ms, moderate between 60 and 80 ms and severe below 60 ms.

The acceleration phase becomes shorter with increased PAP.[10]

Electrocardiography Examination

Electrocardiography (ECG) examination begins with artifact-free ECG recordings, in addition to accurate electrode placement, cleaning of the skin with alcohol and acetone to lower the skin resistance is essential. The standard ECG record consists of 12 "lead" recorded from nine body surface locations with the patient in the supine position.[11]

Statistical Analysis

All data analyzed by repeated measurement, followed by a least significant difference, using the SPSS program version 20. *P*-values of ≤0.05 was considered statistically significant.[12]

Results

Effect of Sildenafil on the Blood Oxygen Saturation (SpO_2) Rate

The blood SpO_2 rate was measured, according to the Sildenafil schedule, there was a significant difference ($P < 0.05$) for all periods (0–15, 0–30, 0–45, 0–60, 0–75, 0–90) in patients' group, compared with the controls' group (Fig. 1).

Effect of Sildenafil on Pulmonary Artery Pressure

This pressure is also measured every 15 days (six times) for both (patients and controls), using the echocardiography. In this study, there was a significant decrease in the PAP ($P < 0.05$) within the time for patients' group, compared with the controls' group (Fig. 2).

Effect of Sildenafil on Tricuspid Regurgitation Pressure

Tricuspid regurgitation was measured, using the echocardiography, it is also assessed with every dose of Sildenafil (six times), there was a significant decrease in this pressure ($P < 0.05$) for the patients treated with Sildenafil, compared with the controls' group (Fig. 3).

Effect of Sildenafil on PA Acceleration Time

In this study, there was a significant increase ($P < 0.05$) in the PAAT, during the period of the treatment, which was 90 days for the patients' treated with Sildenafil, compared with the controls' group (Fig. 4).

Effect of Sildenafil on Electrocardiography Examination

In this study, we measured the R-wave amplitude in V1 and S-wave amplitude in V6, as an ECG parameters. There was a significant decrease in R-wave amplitude in V1 ($P < 0.05$), for the patients treated with Sildenafil, since the mean for R in V1 was 3.383 ± 1.276 on day 0, and 2.697 ± 0.933 after 3 months, compared with non-treated patients (controls' group), while the mean at baseline was 3.875 ± 0.834. No change was found after 3 months, which means no significant difference ($P > 0.05$) in the measurements in the controls' group, compared to the baseline (Fig. 5).

According to the other ECG parameter, S-wave amplitude in V6, there was a significant decrease ($P < 0.05$) in the patients' group, since the mean on day 0 was 4.9302 ± 1.466 and after 3 months, was 3.558 ± 1.007, while in the control group, the mean on day 0 was 3.125 ± 0.834 and after 3 months, was 3.625 ± 1.302, showing no significant difference ($P > 0.05$) in the controls' group (Fig. 6).

Effect of Sildenafil on PCV Measurements

The mean of the PCV for the patients group on day 0 (baseline) was 36.170 ± 13.244 and after 3 months it was increased to 40.581 ± 6.987, while for controls' group the mean of the PCV on day 0 was 36.50 ± 5.071 and after 3 months no difference has been found (35.000 ± 1.772), means that there was a significant increase ($P < 0.05$) in PCV during the period of the treatment, in the patients' group, compared with the controls' group, which showed no significant difference ($P > 0.05$) (Fig. 7).

Effect of Sildenafil on the Blood Film

There was a significant increase ($P < 0.05$) in the rate of the patients with normochromic normocytic blood film,

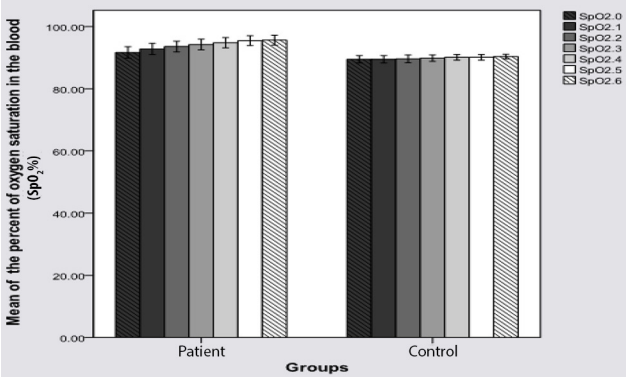

Fig. 1 **Effect of Sildenafil on the blood oxygen saturation rate (SpO_2) for controls and patients' groups, expressed as mean ± SD. $SpO_{2.0}$ = mean of SpO_2 at baseline. $SpO_{2.1}$ = mean of SpO_2 during 15 days. $SpO_{2.2}$ = mean of SpO_2 during 30 days. $SpO_{2.3}$ = mean of SpO_2 during 45 days. $SpO_{2.4}$ = mean of SpO_2 during 60 days. $SpO_{2.5}$ = mean of SpO_2 during 75 days. $SpO_{2.6}$ = mean of SpO_2 during 90 days.**

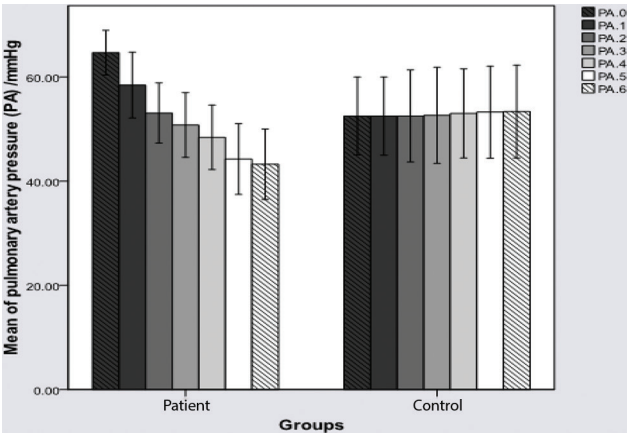

Fig. 2 **Effect of Sildenafil on PAP in mmHg for controls and patients' groups, expressed as mean ± SD. PA.0 = mean of PAP at baseline; PA.1 = mean of PAP during 15 days; PA.2 = mean of PAP during 30 days; PA.3 = mean of PAP during 45 days; PA.4 = mean of PAP during 60 days; PA.5 = mean of PAP during 75 days; PA.6 = mean of PAP during 90 days.**

compared with the controls' group, where no significant difference was found ($P > 0.05$), data are presented in Table 1.

Discussion

In patients with pulmonary or cardiovascular chronic diseases, the level of SpO_2 may drop rapidly due to an increase in pulmonary vascular resistance, chronic hypoxia, and a decrease in lung perfusion.[13]

Effect of Sildenafil on the Blood Oxygen Saturation Rate (SpO_2)

There was a significant increase ($P < 0.05$) in the Sp_{O2} rate in the patients' group, compared with the controls' group, where no significant difference was found ($P > 0.05$), and was consistent with the result of Barreto et al.[14] Our data suggest that Sildenafil has a lowering effect on pulmonary vascular resistance and chronic hypoxia, and also show an increase in the lung perfusion.

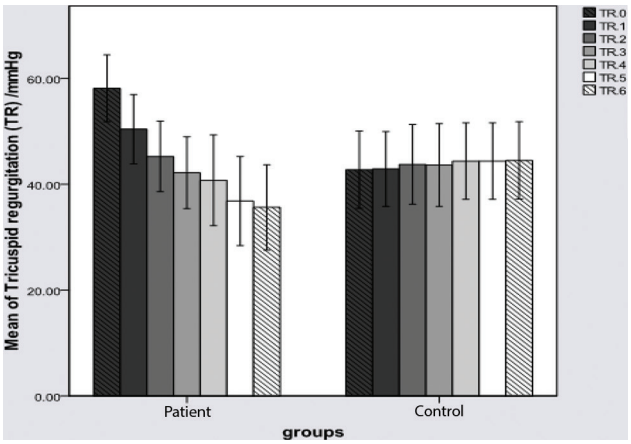

Fig. 3 **Effect of Sildenafil on TR pressure in mmHg for controls and patients' groups, expressed as mean ± SD. TR.0 = mean of TR pressure at baseline. TR.1 = mean of TR pressure during 15 days. TR.2 = mean of TR pressure during 30 days. TR.3 = mean of TR pressure during 45 days. TR.4 = mean of TR pressure during 60 days. TR.5 = mean of TR pressure during 75 days. TR.6 = mean of TR pressure during 90 days.**

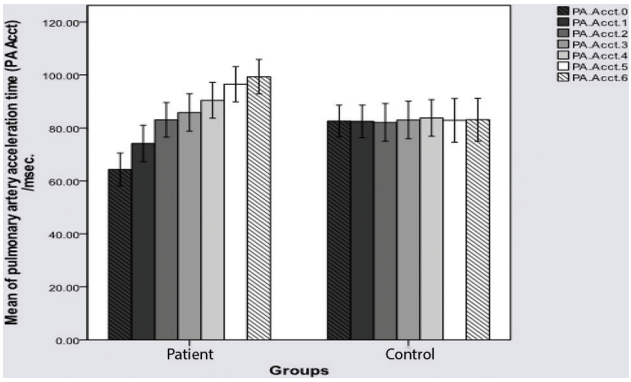

Fig. 4 **Effect of Sildenafil on PAAT in millisecond, for controls and patients' groups, expressed as mean ± SD. PAAT0 = mean of PAAT at baseline. PAAT1 = mean of PAAT during 15 days. PAAT2 = mean of PAAT during 30 days. PAAT3 = mean of PAAT during 45 days. PAAT4 = mean of PAAT during 60 days. PAAT5 = mean of PAAT during 75 days. PAAT6 = mean of PAAT during 90 days.**

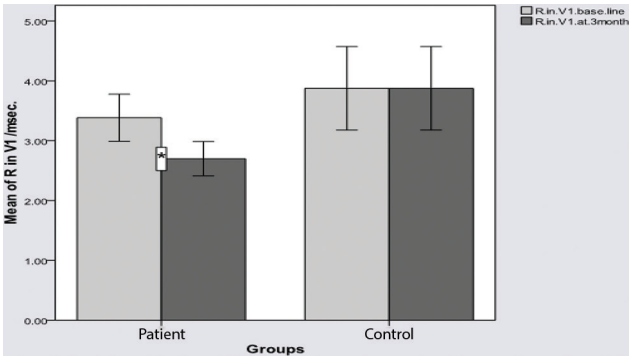

Fig.5 **Changes in the effect of Sildenafil on R in V1 in millisecond for controls and patients' groups, expressed as mean ± SD. *Significant.**

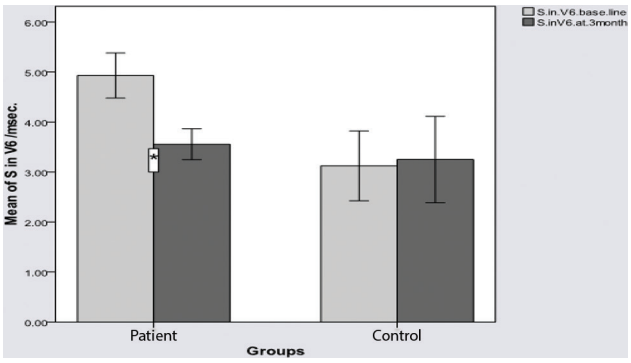

Fig. 6 **Changes in the effect of Sildenafil on S in V6 in millisecond for controls and patients' groups, expressed as mean ± SD. *Significant.**

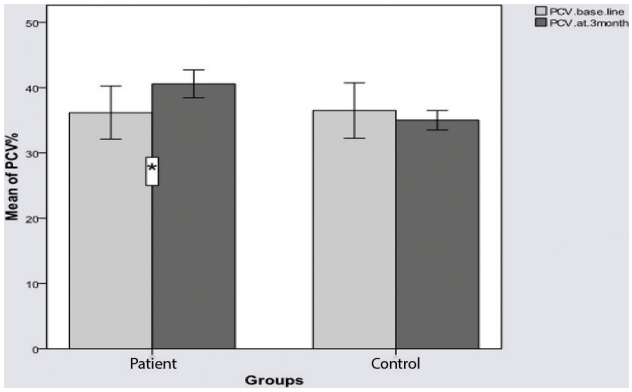

Fig. 7 **Changes in the effect of Sildenafil on percent PCV for controls and patients' groups, expressed as mean ± SD. *Significant.**

Table 1. **The percent of the changes in the results of blood film for both patients and controls' groups**

Results of blood film	0-time	After 3 months	*P*-value	Groups
Normochromic normocytic	60	88	<0.05	
Hypochromic microcytic	23.5	7	<0.05	Patients
Hypochromic normocytic	16.5	5	<0.05	
Normochromic normocytic	50	50	N.S	
Hypochromic microcytic	37.5	37.5	N.S	Controls
Normochromic microcytic	12.5	12.5	N.S	

The values are expressed as a percentage; N.S: non-significant.

Effect of Sildenafil on Hematological Data

After measuring the PCV and examining the blood film as hematological parameters, a significant increase ($P < 0.05$) in the percent of the PCV for acyanotic patients was found, among the patients with normochromic normocytic (normal result of blood films) and a significant decrease in the percent of the PCV for cyanotic heart disease in the patients' group, compared with the controls' group, where no significant difference ($P > 0.05$) was found, and this was consistent with the study of Machado et al.[16] Two types of congenital heart disease exist, cyanotic and acyanotic heart disease. In acyanotic heart disease, the patients with left-to-right shunt, have a physiologic anemia, chronic disorder anemia, nutritional anemia, meaning low PCV. While in cyanotic patients, with right-to-left shunt hypoxia, bone marrow is induced to increase the production of red blood cells with little amount of iron, these patients have high values of PCV (polycythemia).[17] In our study, six (14%) patients had polycythemia. Initial results of this study, as using Sildenafil to treat pulmonary hypertension of congenital heart disease appears promising, by improvement in the arterial oxygenation, as a result of decreasing PAP. This reverses the bone marrow production of red blood cells, leading to lower PCV for cyanotic patients, while the improvement in the nutrition results in an increase in the hematocrit in acyanotic patients. An increase in the hematocrit, greater than 40% can decrease the shunt volume and result in an improvement of symptoms.[17]

Effect of Sildenafil on Echocardiography Data

After 3 months of treatment with Sildenafil, a significant decrease ($P < 0.05$) in PAP and TR pressure and a significant increase ($P < 0.05$) in PAAT, measured by Doppler were found, in patients' group, compared with the baseline. While there was no significant difference ($P > 0.05$) in the values of PAP, TR and PAAT for controls' group, compared with the baseline, this was in agreement with the result of Sastry et al.[18]

These results are confined for the secondary pulmonary hypertension, and they are attributed to the action of Sildenafil on PDE5 enzyme, while, in our study five (11.6%) patients with primary pulmonary hypertension showed no response (no decrease in PAP). However, there was only improvement in their signs and symptoms, suggesting these are a consequence of (1) under development of the lung and pulmonary vascular bed, (2) maladaptation of the pulmonary vascular bed to extrauterine life, because of postnatal stress, and (3) mal-development of the pulmonary vascular bed in utero from an unknown cause, consistent with the result of Andrew et al.[19]

Effect of Sildenafil on Electrocardiographies' Examination

The sildenafil administration had high advantage, since there was a significant decrease ($P < 0.05$) in R in V1 and S in V6, as an ECG parameters in the patients' group, compared with the controls' group. No significant difference ($P > 0.05$) in the controls' group, in comparison with the baseline and this was consistent with the study of Michelakis et al.[20] Patients with pulmonary hypertension mostly have right ventricular hypertrophy (RVH) with right axis deviation, which is a criterion for RVH, high R-wave amplitude in V1 and deep S-wave amplitude in V6, as a very sensitive indicator for RVH.[21]

These results are due to the action of Sildenafil on PDE5 enzyme, leading to a decrease in the PAP, which lead to a decrease in the pressure in the right ventricle.

Conclusion

This study suggested that PDE5 inhibitor (Sildenafil) is useful in patients with secondary pulmonary hypertension, while it has less or negligible effect on the primary pulmonary hypertension.

Conflict of Interest

None.

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