Role of Sildenafil in Treatment of Pulmonary Hypertension in Congenital Heart Diseases for Children in Hilla Province
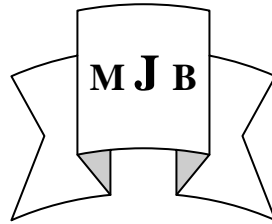
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Abstract

The study was performed to determine the effect of Sildenafil in treatment of pulmonary hypertension in congenital heart disease for children following (15, 30, 45, 60, 75, 90)day administration   of (0.2, 0.4, 0.6, 0.8, 1) mg/kg/dose- 6 times daily. Resulting in a significant decrease ($p<0.05$) in Pulmonary Artery pressure and Tricuspid pressure and a significant increase ($p<0.05$) in percent of oxygen saturation in the blood and Pulmonary Artery Acceleration Time. Result of this study says that sildenafil has a great effect in treatment of the secondary type of pulmonary hypertension and has negligible effect on primary pulmonary hypertension.

دور السلدينافيل في علاج ارتفاع ضغط الشريان الرئوي نتيجة تشوهات القلب عند الاطفال في منطقة بابل

الخلاصة:

هدفت هذه الدراسة الى معرفة دور السلدينافيل في علاج أرتفاع ضغط الشريان الرئوي نتيجة تشوهات القلب الولادية عند الأطفال بعد (١٥،٣٠،٤٥،٦٠،٧٥،٩٠) يوم من أعطاء (٠.٢،٠.٤،٠.٦،٠.٨،١.٠٠) ملغم/كغم/جرعة-٦ مرات باليوم من السلدينافيل والتي نتجت عن أنخفاض معنوي في ضغط الشريان الرئوي والضغط الناتج عن تهدل الصمام الثلاثي ($p<0.05$) وأرتفاع معنوي في نسبة تشبع خلايا الدم بالاوكسجين ووقت تصاعد ضغط الشريان الرئوي ($p<0.05$) وكانت النتيجة أن للسلدينافيل دور كبير وفعال في علاج إرتفاع ضغط الشريان الرئوي الناتج عن تشوهات القلب الولادية عند الأطفال وخاصة النوع الثانوي ولا يوجد له تأثير ملحوظ في علاج أرتفاع ضغط الشريان الرئوي من النوع الأولي.

Introduction

Pulmonary hypertension has been defined as an increased in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest or 30 mmHg during exercise [1]. Which can be classified to Pulmonary arterial hypertension [2]. pulmonary veno-occlusive disease, Pulmonary hypertension due to left heart disease, Pulmonary hypertension due to lung diseases and/or hypoxia, Chronic thromboembolic pulmonary hypertension and pulmonary hypertension with unclear and/or multifactorial mechanisms [1]. Revised classification of pulmonary hypertension are; primary and secondary pulmonary hypertension [3]. The pathological lesions of the disease affect either the distal pulmonary arteries with obstructive proliferation, or septal veins and pre-septal venules, with occlusive fibrotic lesions, lymphatic dilatation and lymph node enlargement, or it could

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be as a thrombi tightly attached to the pulmonary arteries, These may completely occlude the lumen,[4]. The risk factors of pulmonary hypertension includes; heart defects [5]. Hypoxia-Induced Pulmonary Vascular Disease [6]. Lung or thromboembolic diseases [5]. The most frequently symptoms is dyspnea, [7]. And with signs include; right-sided gallop, a palpable right ventricular lift, mid-systolic ejection murmur across the pulmonary valve, increased jugular venous pressure, tricuspid regurgitation [8]. To evaluate this disease we need mainly echocardiographic examination [9]. The treatment of pulmonary hypertension either by Reduce volume overload, Increase cardiac output, Decrease pulmonary vascular resistance and as an examples of newer, successful therapies include prostacyclin analogues (eg, epoprostenol, treprostinil), endothelin antagonists, and phosphodiesterase inhibitors (eg, sildenafil), [10]. According to the congenital heart disease associated with pulmonary hypertension those include; Left to right shunts, like Ventricular Septal Deffect, Increased pulmonary venous pressure, like Mitral Stenosis, Cyanotic heart disease like transposition of the great arteries, Palliative shunting operation like BT shunts,[11]. Sildenafil is an example of newer therapy for pulmonary hypertension, which is a selective inhibitor of phosphodiesterase type 5, first came onto the market in 1998 as an oral treatment for male erectile dysfunction. It act by making relaxation to the pulmonary arteries by slowing down the degradation of cyclic guanosine monophosphate in a dose that did not cause troublesome systemic vasodilatation [12]. Inhibition of phsphodiesterase type 5

by sildenafil may also enhance the platelet antiaggregatory activity of nitric oxide and inhibit thrombus formation, [13]. Sildenafil is rapidly absorbed after oral administration, with a bioavailability of approximately 40%. Maximum serum concentrations occur 0.5 to 2 hours after an oral dose, Sildenafil is highly protein bound (96%) and extensively distributed throughout the body. It is metabolized via the hepatic cytochrome P450 enzyme system, .The elimination half-life of sildenafil is approximately 4 hours in adults. Only about half the ingested dose gets into the systemic circulation because of 'first-pass' metabolism in the liver [14]. The most frequently reported adverse effects with sildenafil include headache, flushing, stomach upset, nasal congestion, diarrhea or urinary tract infection, and rash or dizzines a minor reduction in blood pressure has also been reported in clinical trials, Abnormal vision has been reported in up to 11% of patients [15]. An initial dose of 0.25 to 0.5 mg/kg given orally every 4 to 8 hours is recommended for pediatric patients with pulmonary hypertension, dose titration should be based on response [16]. Ideal therapies for pulmonary arterial hypertension, act by decrease pulmonary vascular resistance, spare the systemic circulation, and increase right ventricular inotropy [17]. Phosphodiesterase type 5 inhibition meets many requirements for an ideal therapy now [18].

Patients and Methods
Patients and controls
The study was conducted in Maternity and Pediatrics Teaching Hospital in Hilla city. A total of 43 pulmonary hypertensive patients (23 males and 20 females) were enrolled in this study, their mean ages(7.322 ±12.265)/month, while the controls

represents the patients who were not treated by sildenafil, they were 8(4 females and 4 males),their mean ages was(22.14 $\pm$ 22.157)/ month. Effect of sildenafil on % of oxygen saturation (SpO2) and pulmonary artery (PA) pressure, tricuspid regurgitation(TR),Pulmonary artery acceleration time(PA ACCT) were considered in those patients and controls.

Study Design

In this study we have two groups patients and controls groups(only the patients group were treated with sildenafil for three month starting with 0.2 mg/kg/dose-six times daily and then the dose was increased 0.2 mg/kg/dose every 15-days), echocardiographic examination which includes (pulmonary artery pressure, Tricuspid regurgitation velocity, pulmonary artery acceleration time) and percent of oxygen saturation (SpO2) were measured every 15-days.

Detection of oxygen saturation (SpO2)

Choose a well perfused finger that best fits in the sensor, Remove nail polish or artificial fingernail, Insert the finger into the finger sensor until the finger touches the finger stop, position the sensor so that the cable rests along the palm of the hand , Hold the connector rather than the cable when connecting or disconnecting the finger sensor to the oximetere . [19].

The   Echocardiographic examination

The pulmonary artery pressure was regarded as normal between 20 - 25mm Hg, mild pulmonary hypertension between 25-40mm Hg, moderate pulmonary hypertension between 40-60mm Hg and severe pulmonary hypertension above 60mm Hg, which was assessed by Doppler echocardiography in three methods

which allows estimation of pulmonary artery pressure ,they are:

1-Measuring tricuspid regurgitation velocity:

This technique supplemented by estimation of right ventricular (RV) pressure from tricuspid regurgitation jet.

Pulmonary artery pressure = RV systolic pressure = 4 (peak velocity)^2 + right aterial (RA) pressure, (RA pressure normal value = 8-10mm Hg)

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.

2-Peak systolic gradient between the right ventricales(RV) and left ventricles(LV):

Is calculated by using modified Bernoulli equation:

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

3-pulmonary artery acceleration time:

Acceleration time is the time interval between the beginning of the flow and its peek velocity, normal $\geq$120msec.,mild between 80-120msec., moderate between 60-80msec,severe below 60msec.

The Right Ventricular Out flow Tract Flow Acceleration Time (RVOT) flow velocity has a characteristic pattern as pulmonary artery pressure increases. The acceleration phase becomes shorter with increased pulmonary artery pressure [20].

Statistical Analysis

All data analyzed by repeated measurement followed by a least significant difference (LSD), by using the SPSS program version (17). P values of less than or equal to 0.05 was considered to indicate statistical significance, while P values more

than 0.05 indicated statistical non significance.

Results

In this study, there was a significant increased(p<0.05) in the percent of the oxygen saturation in the blood (SpO2) for patients group compared with controls group, and there was a significant decrease(p<0.05) in the pulmonary artery pressure and tricuspid regurgitation pressure for patients group compared with controls group were there was non significant difference(p>0.05) in there results. Also there was a significant increase(p<0.05) in pulmonary acceleration time for patients group compared with controls, were there was non significant(p>0.05) difference in there results. Figure (1,2,3,and 4 respectively).
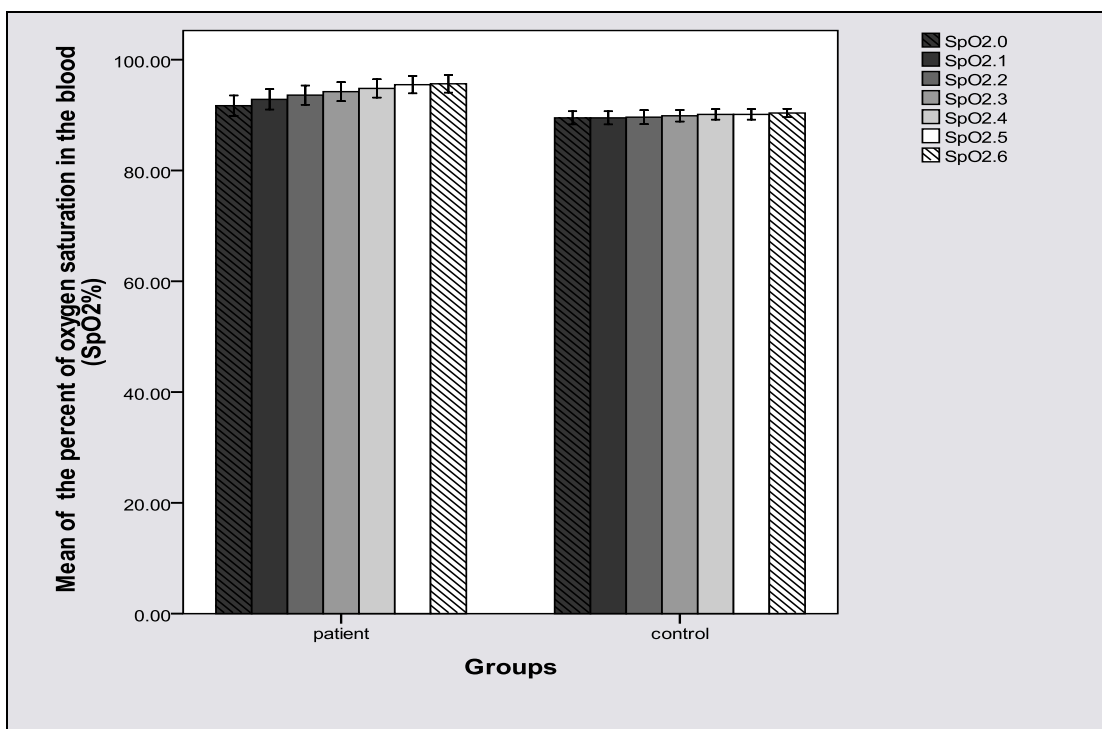

Figure 1 effect of sildenafil on the percent of the oxygen saturation in the blood (SpO2) during the period of the study for the patients compared with the controls group. The values is expressed as mean $\pm$ SD.

SpO2.0=mean of SpO2 at base line.
SpO2.1=mean of SpO2 at 15-days.
SpO2.2=mean of SpO2 at 30-days.
SpO2.3=mean of SpO2 at 45-days.
SpO2.4=mean of SpO2 at 60-days.
SpO2.5=mean of SpO2 at 75-days.
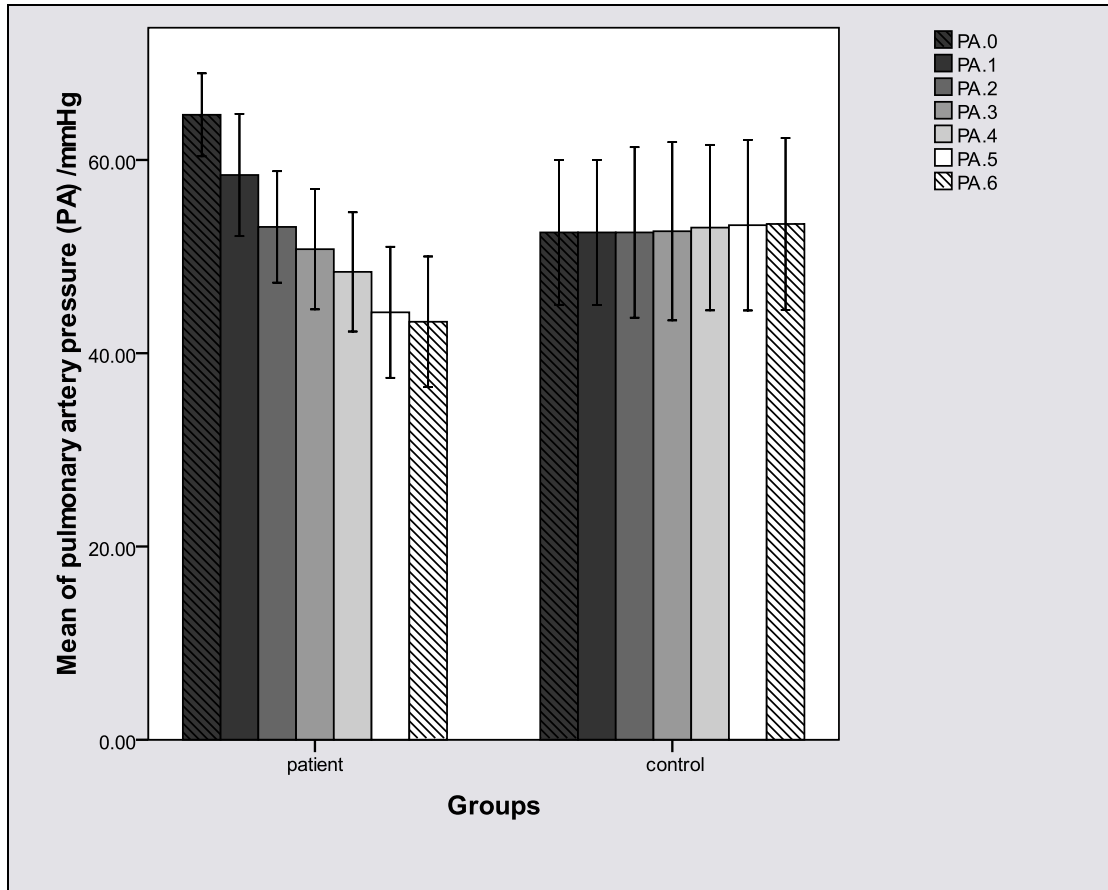SpO2.6=mean of SpO2 at 90-days.

Figure 2 The mean changes of the PA pressure /mmHg during the period of the study for the patients compared with controls group. The value is expressed as mean $\pm$ SD.

PA.0=mean of pulmonary artery pressure at base line.
PA.1=mean of pulmonary artery pressure at 15-days.
PA.2=mean of pulmonary artery pressure at 30-days.
PA.3=mean of pulmonary artery pressure at 45-days.
PA.4=mean of pulmonary artery pressure at 60-days.
PA.5=mean of pulmonary artery pressure at 75-days.
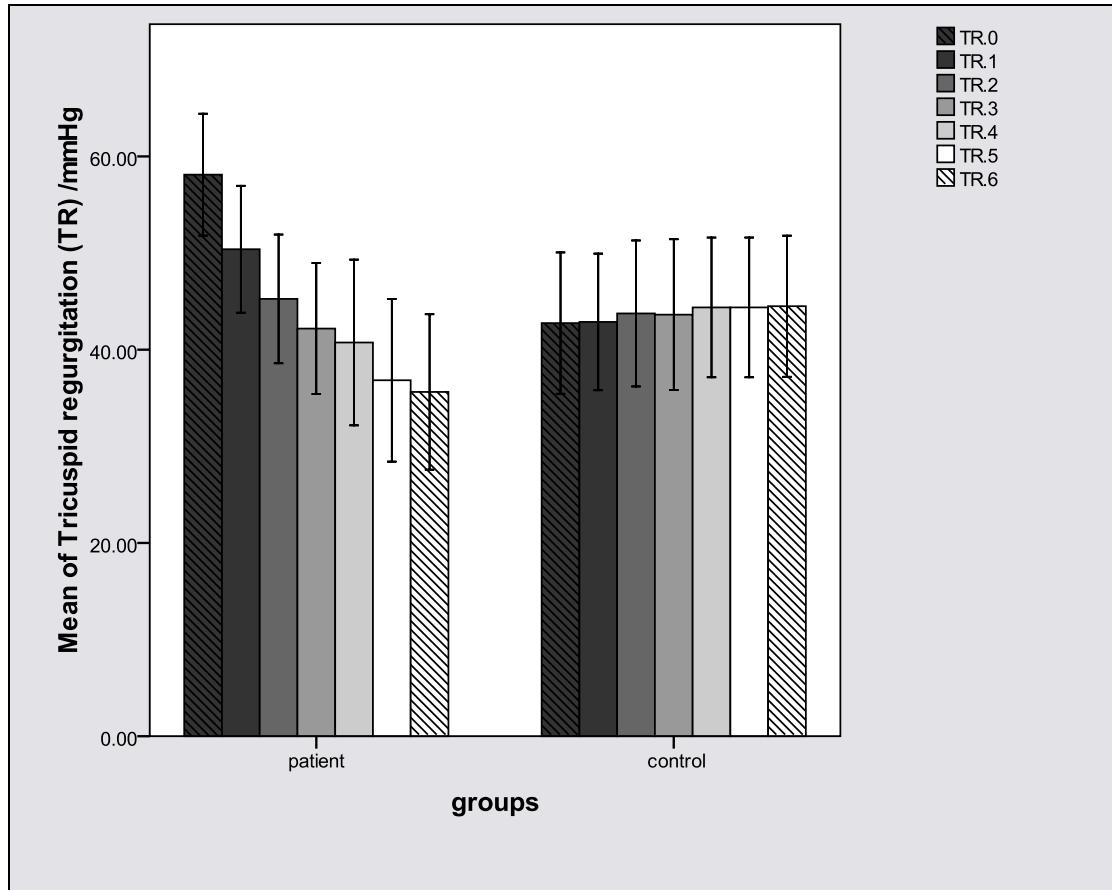PA.6=mean of pulmonary artery pressure at 90-days.

Figure 3 The mean changes of the tricuspid pressure/mmHg during the period of the study for the patients compared with controls groups. The value is expressed as mean $\pm$ SD.

TR.0=mean of tricuspid regurgitation pressure at base line.
TR.1= mean of tricuspid regurgitation pressure at 15-days.
TR.2=mean of tricuspid regurgitation pressure at 30-days.
TR.3=mean of tricuspid regurgitation pressure at 45-days.
TR.4=mean of tricuspid regurgitation pressure at 60-days.
TR.5=mean of tricuspid regurgitation pressure at 75-days.
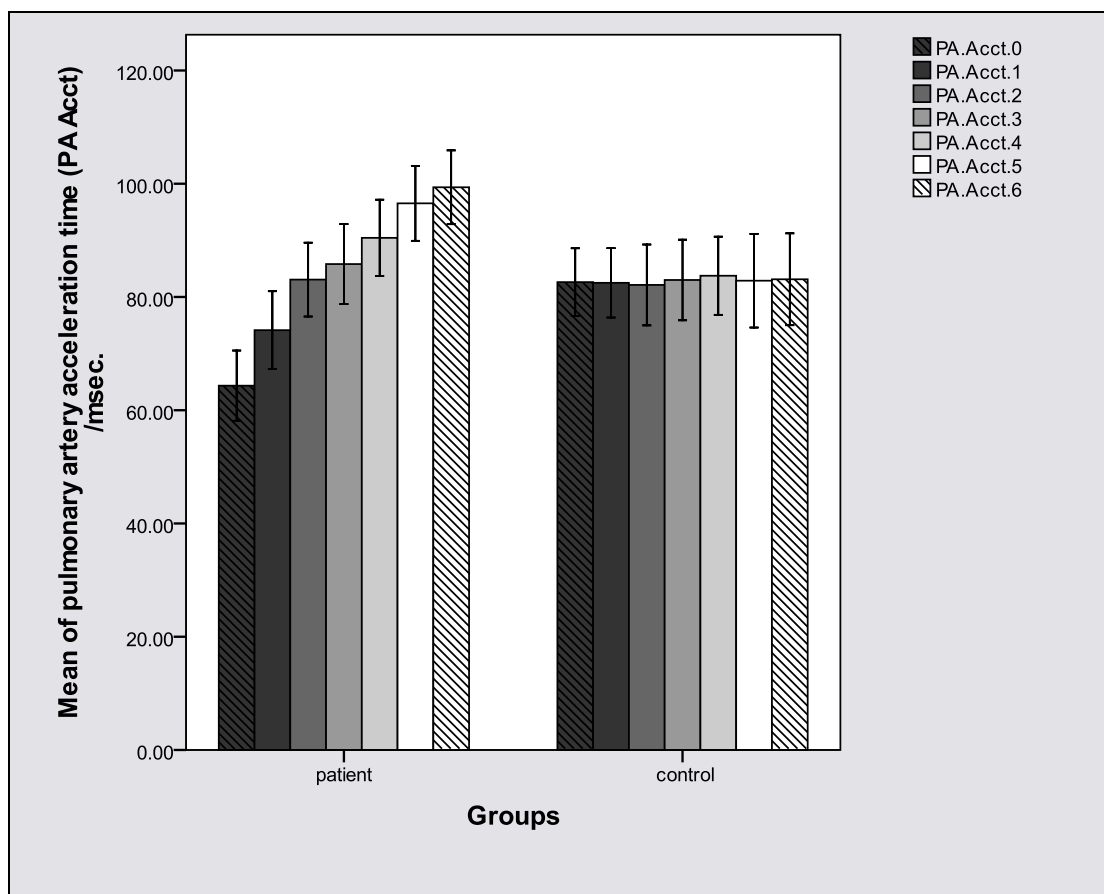TR.6=mean of tricuspid regurgitation pressure at 90-days.

Figure 4 the mean changes of PA ACCT/ msec. during the period of the study for the patients compared with controls group. The value is expressed as mean $\pm$SD.
PA.Acct.0=The mean of pulmonary artery acceleration time at base line.
PA.Acct.1= The mean of pulmonary artery acceleration time at 15-days.
PA.Acct.2= The mean of pulmonary artery acceleration time at 30-days.
PA.Acct.3= The mean of pulmonary artery acceleration time at 45-days.
PA.Acct.4= The mean of pulmonary artery acceleration time at 60-days.
PA.Acct.5= The mean of pulmonary artery acceleration time at75-days.
PA.Acct.6= The mean of pulmonary artery acceleration time at 90-days.

Discussion

When patients have pulmonary or cardiovascular chronic diseases, the level of SpO2 may drop rapidly due to increase pulmonary vascular resistance , chronic hypoxia, decrease lung perfusion ,[21]. In this study there was a significant increase (p<0.05) in the percent of SpO2 for the patients group compared with controls group were there was non significant difference (p>0.05) in there results. and this agreed with,[22]. Our results is due to lowering effect of sildenafil on pulmonary vascular resistance and increase the lung perfusion and decrease chronic hypoxia.

In our study and after three months (90) days of treatment with sildenafil to the patients group, there was a significant decrease(p<0.05) in PA pressure & tricuspid regurgitation pressure and a significant increase (p<0.05) in PA Acct measured by Doppler for patients group compared with the base line, while there was non significant difference(p>0.05) in the values of(PA,TR,PA Acct) for

control group compared with its base line, this is agreed with [23].

These results is confined for the secondary pulmonary hypertension and it is attributed to the action of sildenafil on PDE5 enzyme, while, in our study there was 5 (11.6%) patients with primary pulmonary hypertension show no response (PA-pressure not decrease) there was only improvement in their signs and symptoms this explained by one of three causes; under development of the lung and pulmonary vascular bed, maladaptation of the pulmonary vascular bed to extrauterine life as a result of postnatal stress, maldevelopment of the pulmonary vascular bed in utero from an unknown cause, these results is agreed with[24].

Conclusion

This study suggested that phosphodiesterase type 5 inhibitor (sildenafil) is useful in patients with secondary pulmonary hypertension while it has less or negligible effect on the primary pulmonary hypertension.

Recommendations

1- Patients who are candidates for therapy with sildenafil should receive regular follow up care and should under go a careful clinical assessment by a specialist with experience in pulmonary hypertension.

2- For the future, patients with pulmonary hypertension should under go an invasive hemodynamic studies (catheterization) for proper results.

3- Due to the rarity of the disease, we need long time to increase the number of the patients to give good results.

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