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Comparison between the Effect of Sildenafil versus Nifedipine in the Treatment of Pulmonary Hypertention in Children

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Abstract: Pulmonary Hypertension (PH) is an increase of blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, together known as the lung vasculature, leading to shortness of breath, dizziness, fainting and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure. The aim of this study is to evaluate the effect of sildenafil versus nifedipine in the treatment of pulmonary hypertension in children. The study was carried out on 30 pulmonary hypertension patients (15 males and 15 females), 1 month to 10 years old and their weights ranged from 4 to 28 kg; from outpatient pediatric cardiology clinic at Bani suef university hospital; Patients were divided into two equal groups. Group (A) received sildenafil in a dose of 0.1-1 mg/kg/dose every 8 h orally and group (B) received nifedipine in adose of 0.5-3 mg/kg/dose every 8-12 h orally. Patients were treated and followed for 6 month. They were represented to full history taking, clinical examination, Echocardiographic examination in the beginning and every 6 months of the study. there was an improvement in general health of children after therapy and in respiratory rate, decreasing in pulmonary artery pressure in both groups but, the decrease in P.A.P in group A is greater than group B and the improvement in H.R in group A is better than group B So, we concluded that usage of sildenafil in children with pulmonary hypertension either primary or secondary is better and more effective than usage of nifedipine.

Keywords: Fraction shortening, heart rate, nifedipine, pulmonary artery pressure, pulmonary hypertension, sildenafil

INTRODUCTION

The right ventricle pumps blood returning from the body into the pulmonary arteries to the lungs to receive oxygen. The pressures in the lung arteries (pulmonary arteries) are normally significantly lower than the pressures in the systemic circulation. When pressure in the pulmonary circulation becomes abnormally elevated, it is referred to as pulmonary hypertension, pulmonary artery hypertension, or PAH (Juliana and Abbad, 2005).

Pulmonary hypertension can be classified into primary (idiopathic) or secondary to pulmonary parenchymal disease (such as meconium aspiration syndrome, surfactant deficiency or alveolocapillary dysplasia), severe pulmonary hypoplasia, polycythemia, hypoglycemia, sepsis or maternal ingestion of prostaglandin inhibitor (Adatia, 2002).

Pulmonary hypertension is known by using tricuspid regurgitation jet velocity and the modified Bernoulli equation, with right atrial pressure assumed to be 10 mm Hg, the mean PA pressure was found to be 28.3+/-4.9 mm Hg in infants (Park, 2008).

Sildenafil produces acute and relatively selective pulmonary vasodilatation and this seems to be maintained long term (Erickson *et al*., 2002).

Sildenafil is a selective agent, which relaxes pulmonary vascular smooth muscles. It is a potent specific orally available Phosphodiestrase type 5 (PDE5) inhibitor. It facilitates Nitric Oxide (NO) cGMP induced vasodilatation in the lungs by inhibiting the degradation of cGMP and increasing its cellular levels (Shyam and Bahanu, 2002).

PDE5 is found in high concentration in the lung. The tissue specific distribution of PDE5 makes sildenafil an attractive alternative or adjunct to current therapies (Abrams *et al*., 2000). The terminal half life of sildenafil is three to five hours (Eardley *et al*., 2000). Previous studies have shown that the peak hemodynamic effects of sildenafil occur at about 50 min after oral intake (Jackson *et al*., 1999).

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There are three general approaches using the NO/cGMP pathway to treat PAH:

- Increase supply of exogenous NO
- Increase production of endogenous NO
- Delay the metabolism of NO-induced synthesis of cGMP (Kanki-Horimoto *et al*., 2006)

In the circulation, NO is bound by hemoglobin and biologically inactivated, therefore, Inhaled Nitric Oxide (INO) causes little or no systemic vasodilation or hypotension, INO administrated by conventional or high frequency ventilation in doses of 5-20 parts permillion (ppm) causes pulmonary but not systemic vasodilation and thus selectively decreases PVR (Van Marter, 2008).

PDE-5 is selective for cGMP as substrate and contains a noncatalytic high-affinity PDE-5 cGMP binding site (with unknown function) similar to that of PDE-2 and PDE-6. Convenient sources for purification of the enzyme and testing of inhibitors are porcine or human platelets. These inhibitors are often powerful vasorelaxants, as PDE-5 also occurs in vascular smooth muscle (Watanabe *et al*., 1998).

Several families of PDEs, the enzymes that catalyze hydrolysis of the cyclic nucleoside monophosphates 3'5'cAMP and 3'5'cGMP, have been identified and characterized in recent years (Beavo, 1995). Sildenafil is a potent and selective inhibitor of cGMP-specific PDE-5. This isoenzyme metabolizes cGMP which is the second messenger of NO and a principal mediator of smooth muscle relaxation and vasodilatation. By inhibiting the hydrolytic breakdown of cGMP, sildenafil prolongs the action of cGMP. This results in augmented smooth muscle relaxation (Reffelmann and Kloner, 2003).

The cAMP hydrolyzing PDE-3 and PDE-4 and the cAMP, cGMP hydrolyzing isoform PDE-2, as well as PDE-7 to PDE-11 are inhibited by sildenafil (Senzaki *et al*., 2001).

Nifedipine belongs to a class of medications called Calcium Channel Blockers (CCBs), dihydropyridine derivative with a striking in vivo affinity for arterial smooth muscle. When administrated to normal subject or patient it produce dose- related decrease in peripheral vascular resistance and systemic arterial pressure (McAllister, 1986), that are used to treat angina (heart pain), high blood pressure and abnormal heart rhythms (Nikol *et al*., 1997).

Nifedipine and other dihydropyridines have the greatest peripheral vasodilatory action with little effect on cardiac automaticity, conduction, or contractility (Kaplan, 1992).

Nifedipine works by blocking the flow of calcium into the muscle cells surrounding the arteries that supply blood to the heart (coronary arteries) as well as other arteries of the body. Since the inflow of calcium is what causes the muscle cells to contract, blocking the entry of calcium relaxes the muscles and dilates (widens) the arteries **(**Nikol *et al*., 1997).

PATIENTS AND METHODS

A local hospital research ethics committee approval was obtained for the patients study. Thirty patients were included in the study (15 males and 15 females); their ages ranged from 1 month to 10 years old and their weights ranged from 4 to 28 kg, they were collected from outpatient pediatric cardiology clinic of Beni Suef University Hospital with pulmonary hypertension. The study was conducted during the period of January to June/ 2011. An informed consent was obtained from parents or legal guardians.

Inclusion criteria: Patients diagnosed as pulmonary hypertension.

Exclusion criteria: Patients with pulmonary hypertension admitted to inpatient department with non compromised cardiac condition.

All patients were evaluated by: Detailed history and thorough clinical examination which includes Name, age, sex, weight and Present history, with concentration on shortness of breath with everyday activities, Fatigue., Weakness and Syncope.

Patients were divided into two equal groups A and B. Each group consisted of (15) patients:

- **Group (A):** Represents patients who received sildenafil in the dose of 0.1-1 mg/kg/dose every 8 h orally.
- **Group (B):** Represents patients who received nifedipine in dose of 0.5-3 mg/kg/dose every 8-12 h orally.

All these patients were subjected to:

- Thorough clinical examination every month for six months, which includes:
  - Cardiovascular examination (Heart sounds, heart rate murmur, perfusion and blood pressure)
  - Neurological examination (tone, reflexes, anterior fontanel)
  - Respiratory examination {respiratory rate, retractions (intercostal, subcostal and suprasternal), grunting, cyanosis, nasal flaring, breath sounds and adventitious sounds}
- **Plain chest x-ray examination:** It was done on the start of the study to:
  - Diagnose any lung disease as grades of respiratory distress syndrome, air leak.
  - Determine if there is any cardiomegally.
  - Determine the degree of lung inflation to adjust mean airway pressure.

Echocardiography:

- Vivid 3 pro (General electric) Duplex-pulsed Doppler ultrasound machine with a 10 s MHZ short focus probe and high pass filter at 50 HZ was used.
- Echocardiographic examination included M-mode, 2-D, Doppler and color flow mapping.
- M-mode study was used for measurement of the dimensions of cardiac chambers and vessels, thickness of ventricular septum and free walls, assessment of left ventricular systolic function.
- Two-dimensional echo examinations were performed in the following transducer locations, (parasternal, apical, subcostal and suprasternal notch positions).

It was performed initially before starting treatment to:

- Establish the structural normality of the heart.
- Estimate the ejection fraction and pulmonary artery systolic pressure.

Statistical analysis: A two-way Analysis of Variance (ANOVA) test was used to compare the effect of Sildenafil verses nifedipine on clinical data and Echocardiography examination using SPSS V15.0 (SPSS Inc., Chicago, IL).

Data was summarized as mean and Standard Deviation (SD). p-value was calculated to compare between the two groups, it is considered significant if <0.05.

RESULTS

The study was conducted on 30 (15 females) pulmonary hypertension patients, collected from pediatric Cardiology Clinic at Beni Suef University Hospital. The patients' ages ranged from 1 month to 10 years old and their weights ranged from 4 to 28 kg, Group A mean (S.D.) age is 34.1±35.7 Month. Group B mean (S.D.) age is 25.3±31.0 Month.

In terms of age, weight and sex, all groups were statistically homogenous. Also data analysis of the two groups before the beginning of study showed no significant differences concerning Heart rate, Respiratory rate, Ejection fraction, Fraction shortening and Pulmonary artery pressure.

Table 1: Comparison between before and after treatment (in group A)

	Before mean±S.D.	After mean±S.D.	p-value	Sig.
H.R	150.3±12.3	148.7±12.2	0.136	NS
R.R	48.3±12.3	29±7.4	0.001	HS
F.S	0.4±0.1	0.4±0.1	0.504	NS
P.A.P	53.8±11.1	31.2±6.1	0.001	HS

Table 2: Comparison between before and after treatment in group B

	Before mean±S.D.	After mean±S.D.	p-value	Sig.
H.R	139.7±10.40	147.3±12.10	0.001	HS
R.R	45.7±13.90	38.0±13.20	0.001	HS
F.S	0.3±0.08	0.4±0.08	0.001	HS
P.A.P	55.1±11.50	48.8±11.80	0.030	S

Means and SD of the collected data after therapy of the two groups are shown in Table 1 and 2.

The study showed that the effect of sildenafil in group A is better than the effect of nifedipine in group B on pulmonary artery pressure, heart rate, Respiratory rate and fraction shortening.

In pulmonary artery pressure, there was significant decrease after the sildenafil treatment in group A ($p = 0.001$) and there was significant decrease in group B ($p = 0.03$) (Table 2).

In Fraction Shortening, there was an insignificant difference after sildenafil treatment in group A ($p = 0.504$) and there was significant decrease in group B ($p = 0.001$).

After treatment, there was a significant difference between the two groups regarding the decrease in pulmonary artery pressure where, there was more decrease in P.A.P of patients who received sildenafil than the decrease in P.A.P of patients who received nifedipine.

Also, After treatment, there was a significant difference between A and B groups regarding the clinical improvement in Heart rate and Respiratory rate with p-value 0.038 and 0.029, respectively, where there was better clinical improvement in sidenafil group than nifedipine group, As nifedipine increase Heart rate while sildenafil has no effect on heart rate.

However, there was no significant difference between the two groups, after the six months therapy regarding Fraction shortening with p-value 0.470 (Table 3).

Table 3: Comparison between group A and group B regarding the following parameters

		Group A mean±S.D.	Group B mean±S.D.	p-value	Sig.
Age (month)		34.1±35.7	25.3±31.0	0.481	NS
H.R	Before	150.3±12.3	139.7±10.4	0.506	NS
	After	148.7±12.2	147.3±12.1	0.038	S
R.R	Before	48.3±12.3	45.7±13.9	0.582	NS
	After	29.0±7.4	38.0±13.2	0.029	S
F.S	Before	0.4±0.1	0.3±0.08	0.592	NS
	After	0.4±0.1	0.4±0.08	0.470	NS
P.A.P	Before	53.8±11.1	55.1±11.5	0.762	NS
	After	31.2±6.1	48.8±11.8	0.001	HS

*: p<0.05; **: p<0.01; ***: p<0.0

DISCUSSION

The aim of the study was to evaluate the effect of sildenafil versus nifedipine in the treatment of pulmonary hypertension in children.

Clinical statistics of patients in all 6 months of the study showed a significant decrease in P.A.P after sildenafil therapy for 6 months in group A. These results are similar to Leuchte *et al*. (2004), who compared NO inhalation and oral sildenafil showed that there was a decrease in pulmonary artery pressure and pulmonary vascular resistance after usage of sildenafil.

Also, Gang *et al*. (2009), showed significant decrease in pulmonary artery pressure after treatment with sildenafil. While Mikhail *et al*. (2004), applied sildenafil to 10 patients with pulmonary hypertension. It was found that the cardiac function was improved.

Also, there was a significant decrease in P.A.P after nifedipine therapy for 6 months in group B; these results are similar to Schrader *et al*. (1992), who applied nifedipine to 64 children with pulmonary hypertension. It was found that mean of P.A.P decreased after nifedipine. But, we found that the decrease in P.A.P in sildenafil group was more evident than nifedipine group, as p-value was 0.001 in group A and 0.03 in group B.

In our study, Sildenafil showed no significant effect on Heart rate in group A with p-value 0.136, our results come in agreement with Baquero *et al*. (2006) who found no change in heart rate before and after treatment with sildenafil.

While, nifedipine showed significant increase in heart rate in group B with p-value 0.001 as it reduced the left to right shunt and increased the stroke volume. Berisha *et al*. (1988) study revealed a similar results as they found that, nifedipine significantly increased systemic output and heart rate.

In comparing the effect of sildenafil versus nifedipine on Heart rate, we found that there was asignificant difference between the two groups with p-value 0.038 as nifedipine increase H.R while sildenafil has no effect on H.R.

In group A there was unnoticeable change in Ejection fraction after sildenafil treatment for six months and this lead to fraction shortening become insignificant with p-value of 0.504, while in group B there was a significant increase in fraction shortening after nifedipine treatment with p-value 0.001, due to the increase in ejection fraction and reduction in left ventricular filling pressure. Our results comes in agreement with the study done by Noori *et al*. (2007) who found that sildenafil has no effect on fraction shortening.

Finally the present study concluded that usage of sildenafil in children with pulmonary hypertension either primary or secondary is better, safer and more effective than usage of nifedipine as there was more decrease in pulmonary artery pressure in sildenafil group than nifedipine group and there was no change in heart rate in group A who received sildenafil while in group B there was significant increase in heart rate after usage of nifedipine.

CONCLUSION

Pulmonary hypertension patients in group A who received Sildenafil in dose of 0.1-1 mg/kg/dose every 8 h orally showed more improvement regarding the reduction in pulmonary artery pressure than the second group which received nifedipine in dose of 0.5-3 mg/kg/dose every 8-12 h orally.

That usage of sildenafil in children with pulmonary hypertension either primary or secondary is better, safer and more effective than usage of nifedipine.

Further wider studies are needed to confirm the results of the presented study.

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