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Efficacy and safety profile of PDE-5 inhibitors (sildenafil) in patients with pulmonary arterial hypertension

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ABSTRACT: Introduction: Pulmonary hypertension is defined as a mean pulmonary artery pressure (MPAP) ≥of 25 mm Hg at rest or 30 mm Hg on exercise.Before transplantation there was no specific treatment for pulmonary hypertension, Although there is no cure for PAH, targeted new therapies have been shown to improve a variety of clinically relevant end-points, including survival, functional class, exercise capacity, hemodynamic variables, and Quality of life measures. This study was aimed to assess the efficacy of Sildenafil citrate in patients with pulmonary artery hypertension and to evaluate the safety profile of Sildenafil citrate in the same population.

MATERIAL & METHODS: This was a randomized, double-blind cross-over design study with a 20 mg TDS dose of Sildenafil citrate given for 12 weeks to patients with pulmonary artery hypertension. 32 patients age >18 years with PAH were included in the study.

RESULT: After 12 weeks of study mean increase in 6-minute walking distance was 303.73, mean pulmonary artery systolic pressure was 52, the mean modified BORG index was 4 in GROUP I. There was a significant increase in the mean 6-minute walking distance of 369.86 with a p-value of 0.001 in GROUP II; there was also an improvement in the BORG dyspnea index with a p-value of 0.02. There was not much improvement in declining of pulmonary artery systolic pressure with a p-value of 0.09, all p values were calculated using the student's T-Test. There was also an improvement in NYHA class in GROUP II. Sildenafil therapy in the dosage used was well tolerated, the most adverse effect noted in the study was of headache 27% followed by limb pain, not many life-threatening effects were noted.

Conclusion: It is concluded from the present study that sildenafil is a safe and effective drug in improving clinical statistics of the patient with pulmonary artery hypertension.

Key Word: Pulmonary arterial hypertension, Sildenafil

I. INTRODUCTION

Pulmonary hypertension is defined as a mean pulmonary artery pressure (MPAP) ≥of 25 mm Hg at rest or 30 mm Hg on exercise.[1]PH covers a heterogeneous group of clinical conditions and is classified according to the most recent classification system defined during the fourth World Symposium on PH held in 2008 in Dana Point, CA, US, into five clinical groups with specific characteristics[2]PAH can be idiopathic pulmonary artery hypertension (IPAH), heritable pulmonary artery hypertension (HPAH) or associated with several risk factors or conditions, such as connective tissue disease or congenital heart disease-associated PAH [APAH]. There is an equal prevalence between the sexes in childhood, although in adulthood more women are affected by PAH than men (female: male ratio 1.7:1).[3,4] Dyspnea and fatigue are the leading manifestations of PAH[5]. Pulmonary hypertension is a challenging disease to diagnose accurately and treat. There is often a delay from first symptoms to diagnosis of up to 3 years and the diagnostic process requires invasive investigations. Before transplantation, there was no specific treatment for pulmonary hypertension, but the last two decades have seen significant advances. Although there is no cure for PAH, targeted new therapies have been shown to improve a variety of clinically relevant end-points, including survival, functional class, exercise capacity, hemodynamic variables, and Quality of life measures. This study was aimed to assess the efficacy of Sildenafil citrate in patients with pulmonary artery hypertension and to evaluate the safety profile of Sildenafil citrate in the same population.

II. MATERIAL & METHODS

This was a randomized, double-blind cross-over design study with a 20 mg TDS dose of Sildenafil citrate given for 12 weeks to patients with pulmonary artery hypertension. This study with Sildenafil citrate was conducted in the

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Department of Medicine, Gandhi Medical College and associated Hamidia Hospital, Bhopal from March 2009 to August 2010, patients attending the medical outdoor and cardio clinic was included in the study.

INCLUSION CRITERIA

Patients meeting the following criteria were included for entry into the study; Ambulative patient of either sex or age >18 years, Subjects whose baseline 6-minute walking distance>100 meters and <450 meters are included. Subjects who had pulmonary artery hypertension predicted by CD ECHO pulmonary artery pressure > 25 mmHg or right ventricular systolic pressure/pulmonary artery systolic pressure > 30 mmHg.

EXCLUSION CRITERIA

Patients less than <18 years of age, Patients whose 6-minute walking distance <100 meters and >450 meters were excluded. Patient unable or unwilling to comply with the study requirements.Patient with significant hepatic or renal disorders.Subjects receiving drugs like cytochrome inhibitors like ritonavir, Ketoconazole.

STATISTICAL ANALYSIS

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the presentation of the continuous variables was done as mean ± SD and median values. The association of the variables which were qualitative in nature was analyzed using the Chi-Square test. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software ver 21.0. For statistical significance, the p-value of less than 0.05 was considered as significant.

III. RESULT

Following the 12 weeks randomized study, the effect and safety of sildenafil citrate were studied on patients with pulmonary artery hypertension Total of 32 patients were taken into study out of which 30 completed the study and 2 patients dropped out from the study. A total of 30 patients were randomly assigned. One GROUP (GROUP-I) continued their routine drug-like digoxin and one GROUP(GROUP-II) received sildenafil citrate in 20mg TDS dose plus to continue their routine drugs. Baseline characteristics of the patient were mean 6-minute walking distance was 260.96 with SD ±61.52, mean pulmonary artery systolic pressure was 62.1 with SD ±14.51, mean modified BORG dyspnea index was 4.86 with SD±0.97 and 70% of patient were in NYHA Class III and 29% were in NYHA class II

After 12 weeks of study mean increase in 6-minute walking distance was 303.73, mean pulmonary artery systolic pressure was 52, the mean modified BORG index was 4 in GROUP I. There was a significant increase in the mean 6-minute walking distance of 369.86 with a p-value of 0.001 in GROUP II; there was also an improvement in the BORG dyspnea index with a p-value of 0.02. There was not much improvement in declining of pulmonary artery systolic pressure with a p-value of 0.09, all p values were calculated using the student's T-Test.There was also an improvement in NYHA class in GROUP II.Sildenafil therapy in the dosage used was well tolerated, the most adverse effect noted in the study was of headache 27% followed by limb pain, not many life-threatening effects were noted. No patient left the treatment due to side effects and the patient's compliance was 100%.

TABLE;01 BASELINE CHARACTERISTICS

S.No.			
1	Age		18-70 yrs(mean 40.03 SD 12.62 years)
2	Sex	Male	12
		Female	18
3	WHO Class		2
			3
4	6-MWD		167-360 meters(mean 260.96 SD ±61.52 meters)
5	PASP(mmHg)		40-90 mmHg (mean 62.1 SD ±14.51)
6	BORG SCORE		mean 4.86 SD ±0 .97

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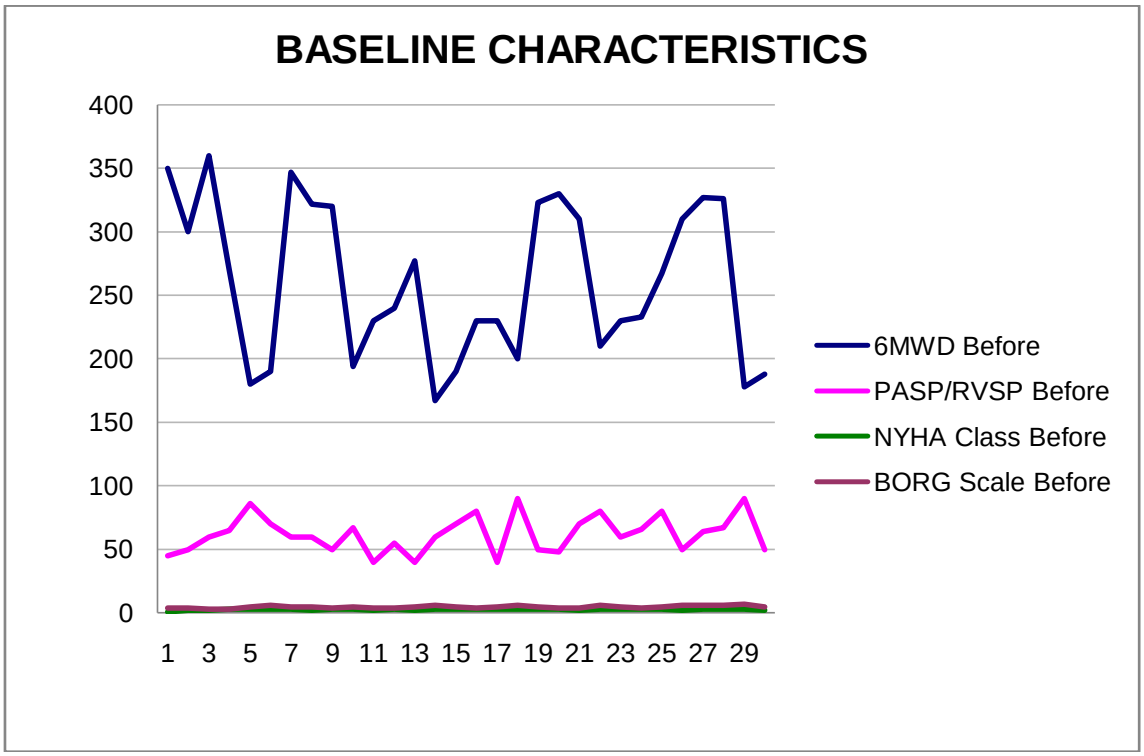

FIGURE 01: BASELINE CHARACTERISTICS

TABLE 02: AFTER 3 MONTH OF THERAPY GROUP-I

S. No	6 MWD	PASP(mmHg)	NYHA class	BORG
Mean	303.7333	52	2.4	4
SD	66.60273	12.85635	0.632456	1.069044968

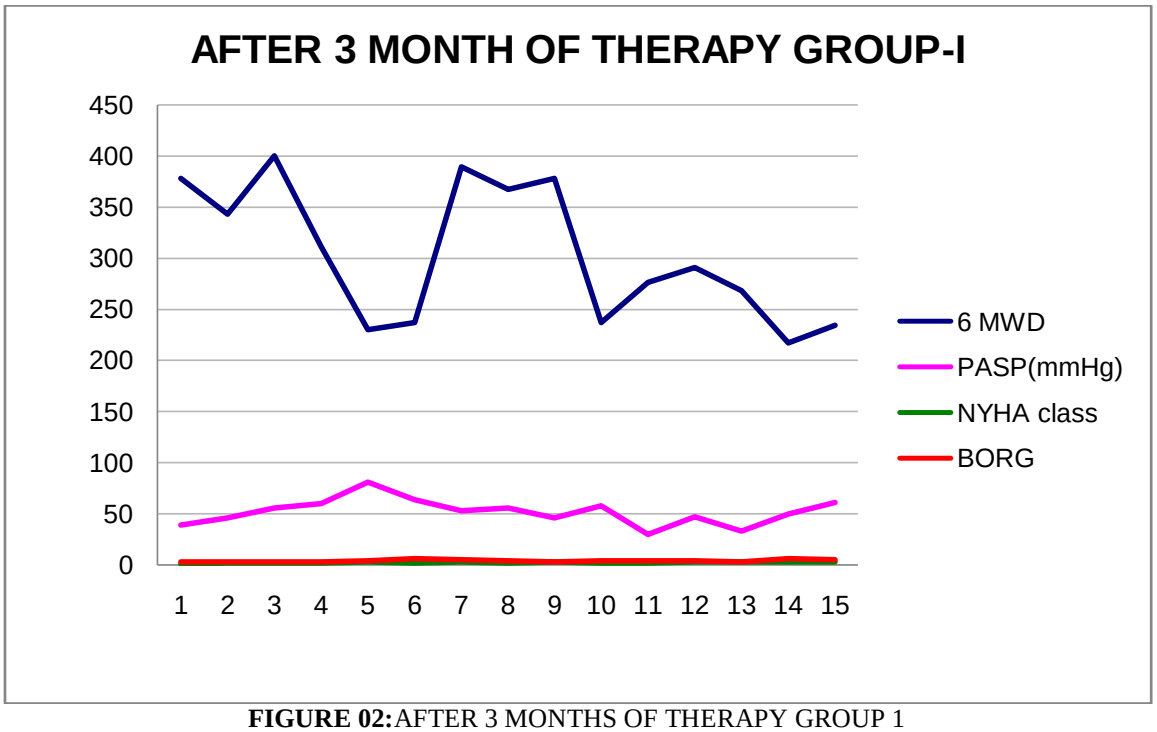

FIGURE 02: AFTER 3 MONTHS OF THERAPY GROUP 1

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TABLE 03: AFTER 3 MONTH OF THERAPY GROUP-II

S. No	6 MWD	PASP(mmHg)	NYHA class	BORG
Mean	369.8667	49.4	2	3.933333
SD	50.64	13.97856	0.377964	0.703732

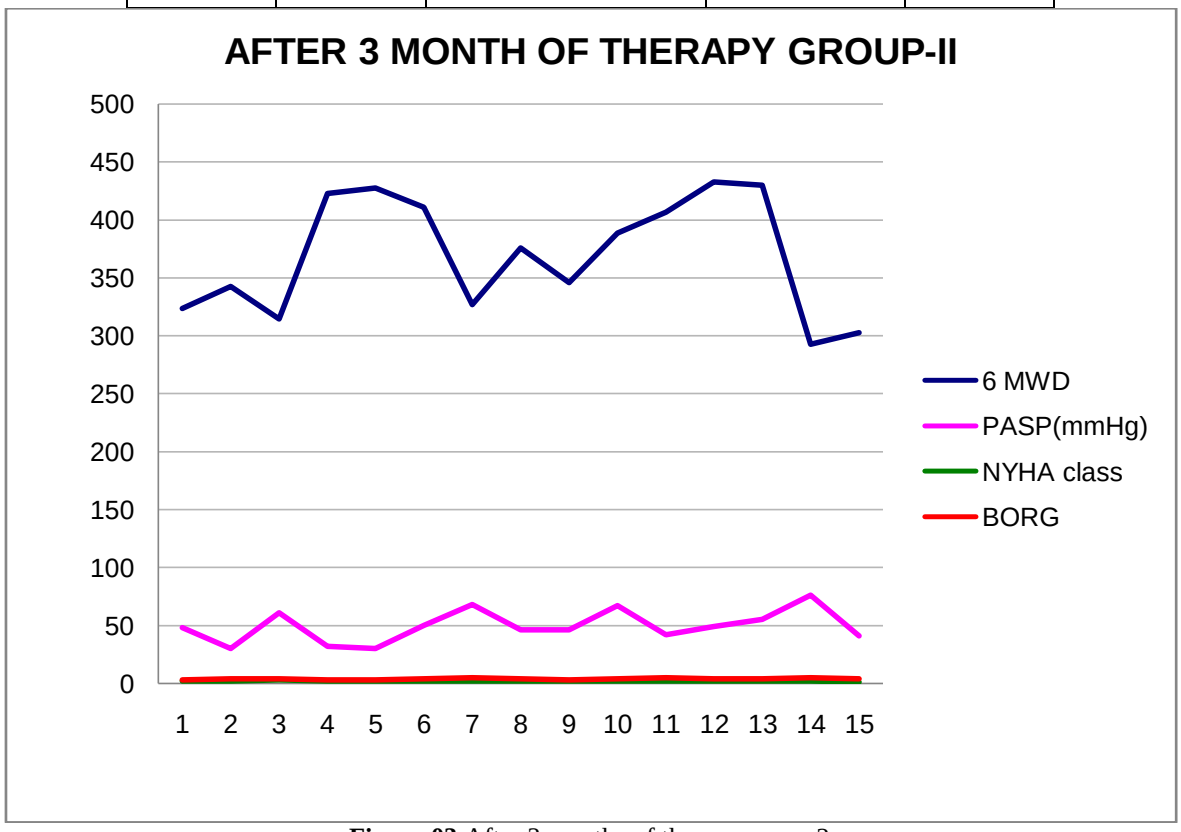

Figure 03 After 3 months of therapy group 2

TABLE 04: OUTCOME MEASURES

S NO	Outcome	Baseline	GROUP I	GROUP II	P-value
1	6 MWD(m)				
	Mean	260.96	303.73	369.86	0.001
	SD±	61.52	66.6	50.64	
2	pulmonary artery systolic				
	pressure mmHg				
	Mean	62.1	52	49.4	0.09
	SD±	14.51	12.85	13.97	
3	modified borg dyspnea				
	index(0-10)				
	Mean	4.86	4	3.93	
	SD±	0.97	1.06	0.7	0.02
4	NYHA class(1-4)				
	Mean				
	SD				
	P-value calculated by student T-Test				

IV. DISCUSSION

Sildenafil has been shown to decrease pulmonary artery hypertension and it increases 6-minute walking distance but most of the studies has been open trial or case review with a small focused group. Stienbellehner et al and Michelakis et al[6,7] showed the benefit of sildenafil on pulmonary artery hypertension and 6-minute walking distance after 5 and 3 months of study. Our study showed that administration of sildenafil in oral form to patients with pulmonary artery hypertension is safe and effective.Michelakis et al[7]Demonstrated that oral sildenafil as a single dose acts as a potent pulmonary vasodilator in patients with both primary and secondary pulmonary hypertension. The 6-minute walking test is an independent predictor of death in a patient with pulmonary artery hypertension and has been used as the primary endpoint in most clinical trials involving a patient with PAH[8,9,10].While there was an appreciable improvement in 6-minute walking distance with reduced exertion but there was not much improvement in pulmonary artery systolic pressure that was similar to the study done by B.K.Sastry et al[11]as compare to other studies which showed improvement in Pulmonary artery hypertension in studies of Chokalingam et al[12], Leuchte HH et al[13], Ng J, Finney SJ, et al[14].

V. CONCLUSION

It is concluded from the present study that sildenafil is a safe and effective drug in improving clinical statistics of the patient with pulmonary artery hypertension.

LIMITATION

The study was conducted on less number of patients further study required with large sample size.

CONFLICT OF INTEREST: None
FUNDING: Nil
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