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Original article

Efficacy of Sildenafil therapy in Paediatrics & Neonates with Pulmonary Artery Hypertension– A study from a Tertiary Care University Hospital

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ABSTRACT

Background: Sildenafil citrate is one of the predominant drugs for treatment of paediatric and neonatal pulmonary artery hypertension (PAH). But there is an uncertainty in the current treatment pattern of sildenafil in children below 8kg body weight.

Methodology: 43 paediatric and neonatal patients treated with sildenafil citrate for PAH were categorised based on their age and evaluated for the safety and the efficacy of sildenafil therapy. Patient demographics, pulmonary artery pressure, echocardiographic reports, drug therapy, adverse effects, World Health Organisation/New York Heart Association (WHO/NYHA) functional class and outcomes were noted. Adverse drug reactions were assessed using WHO & Naranjo's causality assessment scales. Wilcoxon test was used for the comparison of WHO functional class & PAH pre and post sildenafil therapy. A p value of ≤ 0.05 was considered significant. **Results:** PAH associated with congenital systemic to pulmonary shunts (70%) was the major diagnosis observed. There was a significant improvement in the WHO/NYHA functional class pre and post sildenafil therapy from diagnosis Vs discharge ($p < 0.001$), diagnosis Vs first review phase ($p < 0.001$) and the discharge Vs review phase ($p= 0.008$). There were 36 patients with stable and satisfactory outcome, 2 with stable but not satisfactory outcome. 5 patients had unstable and deteriorating outcome resulting in death and the WHO & Naranjo's causality assessments of these cases were unlikely. No side effects to sildenafil therapy were reported. **Conclusion:** In this study the sildenafil doses used were lower than new recommendations and the patients achieved stable and satisfactory outcome.

KEYWORDS: Sildenafil, neonates, paediatrics, pulmonary artery hypertension

INTRODUCTION

Pulmonary artery hypertension (PAH) is a heterogeneous disease characterized by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and premature death, a substantial source of mortality and morbidity in paediatric population [1]. Sildenafil citrate has a promising safety and efficacy profile in the treatment of PAH in adults [2-4]. But in case of neonates, infants and children there is an uncertainty in safety and effective dosage regimen. The recent reports from the randomized controlled trial shows that higher dose of sildenafil can cause mortality in these populations [1, 5].

Hence FDA warns against the use of sildenafil citrate in children up to 17 years of age. The main reason for this warning is a recent study that shows some inconsistencies with the mortality findings, ie. a lower incidence proportion of death in the patients who received placebo in double blind period. Lack of dose response relationship for mortality in long term & inconsistence in relationship between the predicted steady state sildenafil exposure and mortality also strengthen the need for this warning. There is no specific guideline for the use of sildenafil in younger infants with a variety of causes of PAH [1].

PAH has strong relationship with congenital heart disease [6-8]. Surgical correction of these congenital problems alone cannot control PAH in most of the cases. An adjunct oral therapy is needed to make the patient in a safe zone. Here comes the importance of sildenafil citrate for controlling PAH after surgical correction [9,10]. But still there are no specific guidelines in the case of sildenafil therapy for post cardiac surgery, especially in the case of children with below 8 kg body weight [5]. This study was carried out focusing on the utilization of sildenafil citrate in paediatric and neonatal population with PAH.

MATERIALS AND METHODS

This prospective observational study was conducted in a tertiary care teaching hospital with the approval of the Institutional ethics committee and the consent of the care takers of the study participants. A total of 43 patients in neonatal and pediatric age group (0 to 18 years), treated with sildenafil citrate for pulmonary artery hypertension were included in the study from the wards of neonatology, paediatrics and cardiac surgery.

Data Collection & Measurements:

Data on patient demographics, echocardiographic reports, details of surgical procedure, drug therapy, adverse effects, World Health Organisation/New York Heart Association (WHO/NYHA) functional class, [11] and patient outcomes were noted. Modified Ross Heart Failure Classification for Children [12] was used in the case of neonates, infants and small children for evaluating WHO/NYHA functional class. Pulmonary artery pressure was considered as follows: Normal <35 mm of Hg, Mild- 35-50 mm of Hg, Moderate - 50-70 mm of Hg, Severe - > 70 mm of Hg. ADR assessments were done with WHO causality assessment[13] & Naranjo's causality assessment scales [14].

Data Analysis: The collected data were analysed with SPSS 17.0 version. Descriptive statistics (Mean, Standard Deviation) and paired t test were done for bivariate analysis. Wilcoxon test was used for the comparison of pre and post sildenafil therapy, WHO functional class and simultaneous analysis of condition of pulmonary artery pressure in different phases of therapy, WHO functional class and severity of pulmonary artery pressure among each age group. A P value of 0.05 was considered as statistically significant.

RESULTS

A total of 43 patients, prescribed with sildenafil citrate for pulmonary artery hypertension were enrolled for the study. The population was divided according to their age as 14 (32.56%) neonates, 21(48.84%) infants, 6 (13.95%) children and 2 (4.65%) adolescents. Out of 43 patients, majority of them were diagnosed with ventricular septal defect (VSD). PAH associated with congenital systemic to pulmonary shunts (70%) was the predominant class of PAH observed. Among the study subjects, 65% were done with surgical correction for the underlying cause of PAH (Table 1).

Table1: Basic characteristics of study population

Characteristics	Number of Patients (%) (N=43)
Age group	
Neonates (< 1month)	14 (32.56)
Infants (1 month- 1 year)	21 (48.84)
Children (< 12 years)	6 (13.95)
Adolescents (12-18 years)	2 (4.65)
Sex	
Males	25 (58)
Female	18 (42)
Department	
Cardiology & surgery	29 (67.44)
Neonatology	11 (25.58)
Paediatrics	3 (6.98)
Treatment	
Underwent surgery	28 (65 %)
Without surgery	15 (35 %)

Most of the sildenafil prescriptions were with a frequency of three times daily (79 & 80 % respectively). The WHO/NYHA functional class change and the severity of PAH during different phases of therapy such as diagnosis, discharge and in the first review were statistically analysed among the total population. (Table 2).

Table 2: Condition of PAH during different phases of Sildenafil therapy in study population

Condition of PAH at diagnosis n = 43 (%)					Condition of PAH at discharge n = 43 (%)					Condition of PAH at I review n = 38 (%)				
S	M	Mi	NS	D	S	M	Mi	NS	D	S	M	Mi	NS	D
41 (95)	2 (5)	0 (0)	0 (0)	0 (0)	2 (5)	8 (19)	22 (51)	6 (14)	5 (12)	0 (0)	0 (0)	21 (55)	17 (45)	0 (0)

S- Severe; M – Moderate; Mi-Mild; NS- Not Significant; D-Death

During diagnosis 41 (95%) patients had severe PAH and 2 (5%) had moderate PAH. At the time of discharge, 2 (5%) patients had severe PAH, 8 (19%) had moderate PAH, 22 (51%) had mild PAH and 6 (14%) patients had no significant PAH. 5 (12%) patients died during the treatment. At the time of first review there were 38 patients and of this, 21 (55%) patients showed mild PAH in echocardiography and in 17 (45%) patients it was not significant. Both Diagnosis V/s Discharge and Review V/s Diagnosis phases showed a p value of < 0.001** each. The Discharge V/s Review phase showed a p value of 0.008** (Tables 3, 4, 5, 6).

Table 3: WHO/NYHA functional class – pre & post sildenafil therapy in each age group

AGE CATEGORY	WHO/NYHA Functional Class	Number of Patients (N=43)		p value
		Pre- Sildenafil therapy	Post- Sildenafil therapy	
Neonates (n=14)	I	0	12	0.001**
	II	0	0	
	III	0	0	
	IV	14	2	
Infants (n=21)	I	0	16	0.000**
	II	0	3	
	III	0	0	
	IV	21	2	
Children (n=6)	I	0	2	0.038*
	II	0	3	
	III	0	0	
	IV	6	1	
Adolescents (n=2)	I	0	1	0.18 #
	II	0	1	
	III	0	0	
	IV	2	0	

**** Highly Significant at p<0.001,* Significant at p<0.05 and # No Significance**

Table 4: WHO/NYHA functional class during different phases of sildenafil therapy in study population

WHO/NYHA functional class at diagnosis N = 43				WHO/NYHA functional class at discharge N = 43				WHO/NYHA functional class at I review N = 38			
I	II	III	IV	I	II	III	IV	I	II	III	IV
0	0	0	43	31	7	0	5	38	0	0	0

Table 5: Statistical analysis of WHO/NYHA functional class in different phases of sildenafil therapy (N=43)

Study Group	p value
Diagnosis V/s Discharge	< 0.001**
Review V/s Diagnosis	< 0.001**
Discharge V/s Review	0.008**

****** Highly significant

Table 6: Severity of PAH during different phases of drug therapy

Patients with severe PAH before sildenafil therapy	Patients with severe PAH after sildenafil therapy	Patients with severe PAH at first review
41 (95.34%)	7 (16.27 %)	0 (0%)

The outcomes of the patients were categorized as stable and satisfactory, stable but not satisfactory, unstable and deteriorating. There were 36 (84%) patients with stable and satisfactory outcome, 2 (5%) patients with stable but not satisfactory outcome (Table 7). There were 5 (11%) patients with unstable and deteriorating outcome resulting in death (4 patients experienced cardiac failure and 1 patient had cardiac arrest). ADR analysis done for these patients using WHO & Naranjo's causality assessment scales showed an "unlikely" association with sildenafil therapy.

Table 7: Outcome of the patients

Condition of patients after therapy	Number of patients	Percentage (%)	p value
Stable and satisfactory	36	84	**< 0.001****
Stable and not satisfactory	2	5	
Unstable and deteriorating	5	11	

**** Highly significant**

DISCUSSION

PAH is an increasingly recognized life threatening and progressive disorder of neonates and pediatrics with high rate of mortality. In this drug utilization evaluation study we analysed the utilization pattern of Sildenafil citrate for PAH. The present study was done by using the studies of Barst JR et al [1] and Abman HS et al [5] as reference standards.

In the present study, there were 43 patients prescribed with sildenafil citrate therapy for PAH. In 70% of the patients, PAH associated with congenital systemic to pulmonary shunts was the predominant type and surgical repair was performed in 65% of the patients to correct the congenital cardiac problem and then treated with sildenafil citrate. The remaining patients were treated only with sildenafil citrate.

As per FDA recommendations, the dose of sildenafil in paediatrics and neonates is as follows: for < 8 kg patients the dose was 1.5-6 mg/kg/day, for 8kg to 20 kg patients the dose was 10mg three times a day, for patients with > 20 kg body weight the dose was 20mg three times a day [15]. In our study, the dosing of sildenafil was evaluated on the basis of the current official recommendations. The maximum dose used in patients with body weight < 8 kg was 8.3 mg/kg/day and the minimum dose was 0.45 mg/kg/day. In patients with body weight of 8kg to 20 kg, the maximum dose used was 16-15 mg/day and the minimum dose used was 6mg/day. The maximum and minimum doses used were 30mg/day and 25mg/day respectively for patients with body weight of >20kg.

In this study, there was a significant improvement in WHO/NYHA functional class pre and post sildenafil therapy in neonates, infants and children (p= 0.001**, p= < 0.001**, and p=0.038* respectively). But the difference was not statistically significant in adolescents due to poor sample size. Overall these significant improvements in the WHO/NYHA functional class justify the efficacy of sildenafil therapy in improving the cardiac function among this population. The change in PAH was also very significant in the overall population indicating that even when used in low doses, sildenafil had a great role in decreasing severe PAH to mild or non-significant range.

During diagnosis there were 41 patients with severe PAH which reduced to 7 patients at discharge and in the first review it was zero. After sildenafil therapy there were 84% patients with stable and satisfactory outcome. In our study population there was no rebound pulmonary artery hypertension reported with sildenafil therapy.

The recent FDA post market study reported that cardiac failure & cardiac arrest may be an adverse effect associated with sildenafil citrate in PAH therapy in paediatric patients

[15]. Out of 5 patients who died during the study, 2 were prescribed with sildenafil dose lower than recommended, 2 were prescribed with the recommended dose and only one was given with the dose higher than recommended based on the clinical condition. At the time of death, patients had severe PAH and on evaluating the reports of mortality, 4 patients had cardiac failure and 1 had cardiac arrest. But the causality assessment done on these patients using WHO & Naranjo's scales showed an "unlikely" relation between sildenafil citrate and cardiac events related death.

The major limitation of the present study is the lesser number of study population in each age group. A study with a larger sample size can give a clear data regarding the safety, efficacy and dosing of sildenafil citrate in PAH.

CONCLUSION

In this study the sildenafil doses used were lower than new recommendations and patients achieved stable and satisfactory outcome with no side effects. So sildenafil was found to be safe and effective for use in paediatric population. But there are no specific guidelines for dosing of sildenafil for different types of PAH with or without surgical repair. Hence this study strongly recommends the dire need for more specific guidelines for the use of sildenafil especially in neonates & infants with PAH with surgical or non surgical intervention. Further studies are required to examine the long term safety of sildenafil.

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