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Original Article

Examining the Effectiveness of Monotherapy versus Combination Therapy for Pulmonary Hypertension in Patients with Congenital Heart Disease: A Short-Term Outcome Comparison Study

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ABSTRACT

Introduction: *Pulmonary arterial hypertension (PAH) is a serious condition characterized by a gradual increase in pulmonary vascular resistance, which can lead to right heart failure and death. Although the underlying cause of PAH is complex, there are three main pathways involved in the disease: endothelin, nitric oxide, and prostacyclin. Medications that target these pathways have been effective in extending the lives of PAH patients, but the disease remains fatal. Combining different medications is an attractive option for treating PAH, and this study aimed to compare the outcomes of using a single medication versus combining multiple medications over a short period of time.*

Aim of the study: *The study aimed to compare the short-term outcome of monotherapy and combination therapy in the treatment of Pulmonary hypertension*

Methods: *This randomized control trial study was conducted at the Department of Cardiology, Ranpur Medical College, Rangpur, Bangladesh. The study duration was 2 years, from January 2019 to January 2021. During this period, a total of 140 participants were selected for the study following the inclusion, and exclusion criteria from those diagnosed case of pulmonary hypertension with congenital heart disease admitted to the Pediatric Cardiology Department, Bangabandhu Sheikh Mujib Medical University, NICVD, NHF. The selected participants were then divided into two groups of 70 each through random selection.*

Result: *The majority of the participants in this study were between 12 to 15 years of age, with 54.3% in Group A (treated with Sildenafil) and 60.0% in Group B (treated with a combination of medications). Group A consisted of 70 patients, of whom 28 (40.0%) were male and 42 (60.0%) were female. In Group B, 24 (34.4%) patients were male and 46 (65.7%) were female. There were no significant differences between the two groups in terms of mean age or sex. The most common congenital heart defect among the participants was ventricular septal defects (VSD), followed by atrioventricular septal defects (AVSD), and atrial septal defects (ASD). After 3 and 6 months of follow-up, the study found statistically significant differences between the two groups in terms of SpO2 per exercise, 6-minute walk distance, SpO2 after exercise, and alanine aminotransferase. However, there were no significant differences in adverse effects between the two groups. Pulmonary artery systolic pressure (PASP) was significantly reduced in the combination therapy group compared to the monotherapy group.*

Conclusion: *The study found that combining Bosentan with oral Sildenafil medication is a safe and effective treatment for patients with PAH associated with CHD. The combination therapy resulted in significant improvements in clinical status, effort SpO2, exercise tolerance, hemodynamics, and PASP after 3- and 6-month follow-ups. Therefore, the study concludes that combination therapy is more successful than monotherapy for treating PAH associated with CHD.*

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INTRODUCTION

Congenital heart disease (CHD) is a common congenital malformation, comprising over 30% of all birth defects. The heart undergoes a series of developmental steps, starting from a basic muscle structure and eventually forming into a complex four-chambered organ with valves, septa, a conduction system, and arteries. However, any disruption in the normal progression of this development can lead to either structural or functional abnormalities.[1] During fetal development, the lungs receive only 10% of the blood pumped by the heart, while the remaining 90% is diverted to the systemic circulation through the patent ductus arteriosus. However, after birth, the majority of the blood pumped by the right ventricle should flow through the lungs for normal gas exchange. In term newborns, the ductus arteriosus naturally closes within 48-96 hours after birth. Failure of this closure can lead to complications, especially in premature infants.[2] The specific cause of CHD is not fully understood, but several factors have been associated with it, including viral infections in parents, poor maternal nutrition, maternal age over 40, insulin-dependent diabetes, and the use of certain medications like anticonvulsants and lithium. Acyanotic and Cyanotic congenital heart diseases are the most prevalent forms of the condition. Acyanotic heart disease is characterized by several conditions, including ventricular septal defect (VSD), patent ductus arteriosus (PDA), arterial septal defect (ASD), and aortic stenosis (AS).[3] Congenital heart disease has become more prevalent in recent years and is now more common than acquired heart disease. The disease can be fatal during infancy, and some cases may not be identified until later in life.[4] It is essential to determine the prevalence of congenital heart disease, and treatment options include medical therapy, surgery, device closure, and heart transplant.[5] Many individuals born with complex heart abnormalities now reach adulthood and live productive lives. Congenital heart disease refers to any heart disease present at birth, whether discovered at birth or later in life. CHDs are the most common congenital defects, occurring in approximately 8 out of 1000 newborns.[6] If left untreated, individuals with CHD may develop pulmonary arterial hypertension (PAH), particularly those with relevant systemic-to-pulmonary shunts. Eisenmenger syndrome is a congenital cardiac defect that results in severe pulmonary vascular disease and PAH due to a chronic, massive left-to-right shunt, followed by a bidirectional or reversed shunt, cyanosis, erythrocytosis, and various organ involvement.[7 8] Patients with Eisenmenger have a poor quality of life, but the disease progresses gradually, as it does in most cases.[9] They have significantly longer lifespans than individuals with idiopathic PAH and individuals in the same functional class.[10 11] The term "pulmonary hypertension" refers to elevated blood pressure in the pulmonary arterial tree. The main subject of this study is group 1 pulmonary hypertension, which is referred to as pulmonary arterial hypertension (PAH), and is characterized by changes that have a direct impact on the pulmonary vascular. Vasoconstriction, smooth muscle cell, endothelial growth, and intravascular thrombosis are a collection of illnesses that have disparate outward manifestations but are thought to share a common etiology.[12] The diagnosis of pulmonary hypertension is usually delayed, necessitating a comprehensive physical examination to exclude other diseases and determine the most likely cause. For determining whether individuals would benefit from calcium channel blockers, the vaso-reactivity test is crucial.[13] Some facilities use cardiopulmonary exercise testing, which could be helpful. Following a PAH diagnosis, a variety of actions are frequently taken to monitor progress. A number of general measures are suggested for PAH.[14] First, it is advised that conditions where there is an associated cause, such as sickle cell anemia, be optimized. Lifestyle recommendations include things like restricting exercise to prevent symptoms, offering advise on family planning, and preparing for surgery or anesthesia if necessary.[15] The use of oxygen therapy is advised in cases of hypoxemia. Additionally, it should be taken into account when flying because the low cabin pressure can result in dyspnea. During exercise, the pulmonary vascular bed can typically withstand increases in blood flow thanks to dilating and recruitment of underutilized

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vasculature. This ability is diminished in PHTN, leading to an increase in pulmonary artery pressure. Inability to increase cardiac output in response to increases in oxygen demand can cause dyspnea and syncope. Young children are more likely to experience exertional and postexertional syncopal episodes, which show a lack of cardiac output correction and reduce cerebral blood flow. The study aimed to examining the effectiveness of monotherapy versus combination therapy for Pulmonary Hypertension in patients with congenital heart disease.

METHODS

This randomized controlled trial was conducted at the Department of Cardiology, Rangpur Medical College Hospital, Rangpu, Bangladesh with a study duration of 2 years, from January 2019 to January 2021. A total of 140 participants were selected for the study, meeting the inclusion and exclusion criteria for pulmonary hypertension associated with congenital heart disease. The participants were divided into two groups, with 70 patients in each group. Group A received Sildenafil as monotherapy treatment, while Group B received both Sildenafil and Bosentan as combination therapy. The outcomes of the patients were measured using saturation of Oxygen (SPO2) and a six-minute walking distance (6MWD). Clinical data were reviewed, taking into consideration the total number of cases with congenital heart disease, age, sex distribution, and type of CHD. The study group underwent routine investigations such as chest X-ray, electrocardiography, and echocardiography, and the final diagnosis was confirmed by cardiac catheterization. The patients were clinically evaluated every three months for a minimum of six months, and liver enzyme levels were measured every three months. To protect confidentiality and anonymity, each patient was assigned a special ID number that was followed at every step of the procedure. Informed consent was obtained from each patient after explaining the nature, objective, procedure, risks, benefits, and implications of the study. Ethical clearance for the study was taken from the Institutional Review Board (IRB) of BSMMU, and permission for the study was taken from the concerned department. The Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses, and the mean values were calculated for continuous variables. Frequencies and percentages were used to indicate quantitative observations, and the Chi-square test and Unpaired t-test were used for the analysis of qualitative and quantitative variables, respectively. A p-value of less than 0.05 was considered significant. The inclusion criteria for the study included patients aged less than 18 years with pulmonary hypertension associated with congenital heart disease who had given their consent to participate, while exclusion criteria included patients with idiopathic pulmonary hypertension, persistent pulmonary hypertension of newborns, extremely morbid patients, and patients unwilling to participate.

RESULTS

Table 1: *Distribution of demographic characteristics in two groups (N=140)*

Demographic characteristics	Group A (n=70) No. (%)	Group B (n=70) No. (%)	P value
Age			
< 8	8(11.4%)	12 (17.1%)	**<0.5**
8-11	0 (0%)	0 (0%)	
12-15	38 (54.3%)	42 (60.0%)	
16-18	24 (34.3%)	16 (22.9%)	
Age (years) mean±SD	16.4±3.97	14.81±4.12	
Gender			
Male	28 (40.0%)	24 (34.3%)	>0.5
Female	42 (60.0%)	46 (65.7%)	
Male: Female ratio	01:01.5	01:01.9	
Socioeconomic status			
Lower middle class	42 (60.0%)	50 (68.6%)	>0.5
Middle class	24 (34.3%)	18 (25.7%)	
Upper class	4 (5.7%)	2 (5.7%)	

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Data were expressed as frequency, percentage, and Mean±SD

Unpaired student t-test was performed for quantitative variables, and the Chi-square test was used for qualitative variables

Among the participants of group A, a majority (54.3%) belonged to the age group of 12-15 years, which was similar to those from group B (60%). 34.3% of Group-A and 22.9% of Group-B participants had been from the oldest age group of 16-18 years. The mean age of the participants was 16.4 years in Group-A, and 14.81 years in Group B. This difference was not statistically significant. Male: female prevalence was similar in both groups, with higher female prevalence overall. The male: female ratio was 1:1.5 in group-A, and 1:1.9 in group B. The difference between them was not statistically significant. The majority of the participants of the present study, 60% from group-A, and 68.6% from group B were from lower middle socioeconomic classes, with no significant difference between the groups.

Table 2: *Type of congenital heart disease between two groups (N=140)*

Congenital heart disease	Group A (n=70) No. (%)	Group B(n=70) No. (%)	P-value
Atrial septal defect (ASD)	10 (14.3%)	12 (17.1%)	
Ventricular septal defect (VSD)	24 (34.3%)	20 (28.6%)	
Patent ductus arteriosus (PDA)	8 (11.4%)	6 (8.6%)	
Aortopulmonary window	4 (5.7%)	2 (2.9%)	>0.5
Aortic Stenosis	2 (2.9%)	0 (0.0%)	
Single ventricle	4 (5.7%)	4 (11.4%)	
TAPVC with Obstruction	4 (5.7%)	2 (5.7%)	
Atrio-Ventricular Septal Defect (AVSD)	14 (20.0%)	9 (25.7%)	
Total	70 (100.0%)	70 (100.0%)	

Figures in the parentheses indicate the corresponding percentage;

Chi-squared Test (χ^2) was done to analyze the data.

Among the participants of both groups, Ventricular Septal Defect (VSD) had the highest prevalence, observed in 34.3% of group-A, and 28.6% of group-B participants. Following this, the second highest prevalence was observed in terms of Atrio-Ventricular Septal Defect, observed in 20% of group-A, and 25.7% of group-B participants. Some other common congenital heart diseases observed among group-A participants were ASD (14.3%), PDA (11.4%), Aorto-Pulmonary Window (5.7%), Single Ventricle (5.7%), and TAPVC with obstruction (5.7%). Among group B, these congenial heart diseases were of similar prevalence, with no significant difference between the two groups.

Table 3: *Comparison of baseline clinical status, exercise tolerance, and biochemical parameters between two groups at baseline (N=140)*

Variables	Group A (n=70) Mean±SD	Group B (n=70) Mean±SD	p-value
Clinical status			
SpO2 (%) Pre-exercise	80.21±9.2	82.12±8.3	**<0.5**
Exercise tolerance (6MWT)			
Distance (m)	293.1±68.3	360.8±51.3	**<0.5**
SpO2 post-exercise (%)	63.2±15.2	72.6±10.7	**<0.5**
Biochemical parameters			
Aspartate aminotransferase (U/l)	19.6±6.12	18.3±7.11	>0.5
Alanine aminotransferase (U/l)	28.2±9.3	30.1±12.4	**<0.5**

Data were expressed as mean±SD

An unpaired student t-test was performed to compare between two groups

At baseline, there was no significant difference between the two groups in regard to clinical status, exercise tolerance, and biochemical parameters. The pre-exercise mean value of SpO2 was 80.21%

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in group A, and 82.12% in group B. 6MWT test showed that the mean distance was 293.1 meters in group A, and 360.8 meters in group B at baseline, with no significant difference. SpO2 after exercise was 63.2% in group A, and 72.6% in group B. Biochemical parameters were also similar at baseline between the two groups.

Table 4: *Comparison of Clinical status, exercise tolerance, and biochemical parameters after 3 months between two groups (N=140)*

Variables	Group A (n=70) Mean±SD	Group B (n=70) Mean±SD	P value
Clinical status			
SpO2 Pre-exercise	78.6±8.1	84.13±9.23	**<0.5**
Exercice tolerance (6MWT)			
Distance (m)	301.2±72.1	372.4±82.3	**<0.5**
SpO2 post-exercise (%)	64.13±14.6	74.12±11.1	**<0.5**
Biochemical parameters			
Aspartate aminotransferase (U/l)	19.13±61	18.6±7.1	>0.5
Alanine aminotransferase (U/l)	28.36±9.2	32.14±12.6	**<0.5**

At the 3-month follow-up after the start of treatment, the study observed that mean SpO2 pre-exercise was significantly higher at 84.13% among group B participants, compared to 78.6% among group A participants. At the 6MWT test, a significantly higher mean distance was observed among group B participants, as was SpO2 post-exercise. In regards to biochemical parameters, Aspartate aminotransferase did not have any significant difference between the two groups but mean Alanine aminotransferase was significantly higher among group-B participants.

At the 6-month follow-up after the start of treatment, SpO2 Pre-Exercise, 6MWT distance, and SpO2 post-exercise had all been significantly higher among group-B participants.

The adverse effects of both groups were recorded in the study, and no significant association was observed between the two groups. However, upper respiratory tract infection and vomiting had a higher prevalence in group A participants

Table 5: *Comparison of Clinical status, exercise tolerance, and biochemical parameters after 6 months between two groups (N=140)*

Variables	Group (n=70) Mean±SD	Group B(n=70) Mean±SD	P value
Clinical status			
SpO2 (%) Pre-exercise	80.2±8.3	86.28±8.54	**<0.5**
Exercice tolerance (6MWT)			
Distance (m)	311.2±78.0	381.5±83.8	**<0.5**
SpO2 post-exercise (%)	66.4±13.8	77.21±12.3	**<0.5**
Biochemical parameters			
Aspartate aminotransferase (U/l)	20.21±6.2	21.12±8.3	>0.5
Alanine aminotransferase (U/l)	32.37±9.1	35.8±13.8	**<0.5**

Table 6: *Association of adverse effects in two groups (N=140)*

Adverse effects	Group A (n=70) No. (%)	Group B (n=70) No. (%)	P value
Upper respiratory tractinfection	52 (74.3%)	44 (62.9%)	**<0.5**
Vomiting	66 (94.3%)	60 (85.7%)	**<0.5**
Headache	54 (77.1%)	60 (85.7%)	**<0.5**
Bronchitis	22 (31.4%)	26 (37.1%)	>0.5
Pyrexia	10 (14.3%)	14 (20.0%)	>0.5
Pharyngitis	6 (8.6%)	10 (14.3%)	**<0.5**
Cough	12(17.1%)	16 (22.9%)	>0.5
Diarrhea	6 (8.6%)	8 (11.4%)	>0.5
Nasopharyngitis	4 (5.7%)	2 (2.9%)	>0.5

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ECG findings of the pulmonary artery systolic pressure (PASP) showed that among the group-A participants, 40% had been severe cases, 31.40% had been moderate cases, and only 28.60% had

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been mild cases. This was significantly different from the findings of group-B participants, where 65.70% had been mild cases, 25.70% had been moderate cases, and only 8.60% had been severe cases.

Table 7: *Association of echocardiographic findings between groups (N=140)*

Echocardiographic findings (PASP)	Group A (n=35) No. (%)		Group B (n=35) No. (%)		P value
Mild	20	28.60 %	46	65.70 %	
Moderate	22	31.40 %	18	25.70 %	
Severe	28	40.00 %	6	8.60 %	<0.5
Mean±SD	56.15±11.24		38.35±10.12		

DISCUSSION

The study involved 140 participants, who were randomly assigned to either Sildenafil monotherapy (Group A) or the combination of Sildenafil and Bosentan (Group B), with 70 individuals in each group. The majority of patients were in the age range of 12-15 years, representing 54.3% of Group A and 60.0% of Group B. In Group A (the Sildenafil group), there were 28 (40.0%) male and 42 (60.0%) female patients, while in Group B (the combined group), there were 24 (34.4%) male and 46 (65.7%) female patients. Randomization of participants resulted in no significant differences in sociodemographic characteristics between the two groups. The most common congenital heart defect among the participants in both groups was ventricular septal defect (VSD), with 34.3% in Group A and 28.6% in Group B. Atrial ventricular septal defect (AVSD) was the second most common with 20% in Group A and 25.7% in Group B, followed by atrial septal defect (ASD) with 14.3% in Group A and 17.1% in Group B. Randomization of group selection ensured no significant difference between the two groups. After three and six months of follow-up, several clinical variables, including exercise tolerance and biochemical parameters such as SpO2 pre-exercise, 6MWD, SpO2 post-exercise, and alanine aminotransferase showed statistically significant differences between the single (Group A) and combined (Group B) therapy groups. The results of this study showed better outcomes compared to a study by Durongpisitkul et al., who found that 50% of their study participants experienced clinical worsening within 12 months of starting treatment.[16] Durongpisitkul et al. observed that patients who received bosentan monotherapy had a significantly lower risk of clinical worsening compared to those who received sildenafil, with the bosentan group having lower rates of clinical worsening at both 12 months (16.7% vs. 38.3% and 71.4%, respectively) and 24 months (16.7% vs. 61.7% and 77.1%, respectively) (p=0.007). After failing initial monotherapy, 33 patients were given sequential combination therapy. The mean 6MWD significantly increased from 208.9 ± 67.2 m to 285.5 ± 92.1 m after the addition of the second drug at 1 month ($p<0.05$), and further increased to 326.3 ± 62.7 m at 3 months ($p<0.5$), which is consistent with the findings of the present study. These findings suggest that at 3 and 6 months, patients who got Sildenafil monotherapy were more likely to develop clinical deterioration than those who received Sildenafil and Bosentan in combination therapy. Similar findings emerged from a retrospective analytical investigation as well.[17] However, a trial with individuals who had Eisenmenger syndrome revealed that bosentan monotherapy was not more effective than upfront combined therapy with sildenafil for changes in 6MWD.[18] Therefore, the fundamental therapeutic approach is to monitor clinical deterioration and analyze it to determine whether to step up treatment. It has been demonstrated that one of the most effective approaches for treating patients with PAH is one that is goal-oriented and focused on indicators of better survival.[19] [20] Because our study first assessed the effects of add-on sildenafil medication in CHD-related PAH patients demonstrating clinical worsening following oral bosentan, the efficiency of our results was likely superior than that of Iversen et al.'s. In our population, clinical improvement was shown at both the 3-month and 6-month follow-ups. Therefore, the fundamental therapeutic approach

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is to monitor clinical deterioration and analyze it to determine whether to step up treatment. It has been demonstrated that one of the most effective approaches for treating patients with PAH is one that is goal-oriented and focused on indicators of better survival.[19 20] Because our study first assessed the effects of add-on sildenafil medication in CHD-related PAH patients demonstrating clinical worsening following oral bosentan, the efficiency of our results was likely superior than that of Iversen et al.'s. In our population, clinical improvement was shown at both the 3-month and 6-month follow-ups. In the treatment of PAH in infants and children, the usage of Sildenafil and Bosentan has demonstrated potential advantages and better patient outcomes. Analysis reveals a substantial difference in PASP-related echocardiographic findings between the two groups. When compared to the monotherapy group, PASP dramatically lowered in the combined group. The results of Pan et al. corroborated these conclusions.[21]

LIMITATIONS OF THE STUDY

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

According to the findings of this study, combination therapy is more effective than monotherapy in treating PAH with CHD. Our results show that the combination of oral Sildenafil and Bosentan in patients with CHD-related PAH is safe, well-tolerated, and results in a significant improvement in clinical status, effort SpO2, exercise tolerance, hemodynamics, and PASP at 3- and 6-month follow-ups.

RECOMMENDATIONS

To determine the appropriate posology of Sildenafil and to determine its position in upcoming advancements and therapies in the field of pediatric cardiology, more study is required. In the present monitoring plan and flow-chart, careful patient management is advised for changing the dose schedule in case of high liver function tests or serious adverse effects.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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