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Original Research Article

Comparison of adverse effects in the treatment of pulmonary hypertension with monotherapy and combination therapy

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a serious condition characterized by an increase in pulmonary vascular resistance (PVR) that leads to right heart failure and death. The study aimed to compare the side effects of monotherapy and combination therapy in the treatment of pulmonary hypertension
Methods: This randomized control trial study was conducted at the department of pediatric cardiology, Bangabandhu Sheikh Mujib medical university, national institute of cardiovascular disease, and national heart foundation, Dhaka, Bangladesh. The study duration was 1 year, from January 2018 to December 2018. During this period, a total of 70 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.
Result: Maximum patients had ventricular septal defects (VSD) (34.3% in group A, and 28.6% in group B). Followed by AVSD. 20.0% in group A and 25.7% in group B. Atrial septal defect (ASD) were 14.3% in group A, and 17.1% in group B. After three, and 6 months of follow-up SpO_2 per exercise, 6MWD, SpO_2 post-exercise, and alanine aminotransferase showed statistically significant differences between single and combined groups. There was no statistically significant difference regarding adverse effects between the 2 groups, but group B patients had slightly higher incidence of some side effects. PASP was significantly decreased in combined group than monotherapy group.
Conclusions: This study concludes that combination therapy is more successful than monotherapy in PAH with coronary heart disease (CHD). Our findings demonstrate that combining Bosentan with oral Sildenafil medication in patients with CHD-related PAH is safe, and well tolerated at 3-, and 6-month follow-ups, resulting in a significant improvement in clinical status, effort SpO_2, exercise tolerance, hemodynamics, and PASP.

Keywords: Sildenafil, Hypertension, Monotherapy, Combination Therapy, Cardiac, PAH

INTRODUCTION

Coronary heart disease (CHD) is the most common birth condition, accounting for more than 30 percent of all congenital abnormalities. The heart grows from a primitive muscle wrapping to a four-chambered muscular organ with septa, valves, a conduction system, and main arteries beginning and ending in the heart during development. Any imperfection in the orderly and sequential progression of development culminates in structural or functional abnormalities.[1] The lungs receive 10% of the cardiac output throughout intrauterine life. The remaining 90% is sent to the aorta and systemic circulation through the patent ductus arteriosus. After birth, the majority of the right ventricular output should pass via the lungs to enable normal gas exchange. In term babies, ductus constriction and functional closure occur immediately after birth to accomplish this. The ductus arteriosus closes in term babies in 48 hours and nearly fully in 96 hours. Complications arise when this natural closure fails, especially in pre-term newborns.[2] Although

the actual cause of CHD is unknown, several variables have been related to it, including parental viral infection, poor maternal nutritional status, mother's age over 40, insulin-dependent diabetes, and use of medications such as lithium, anticonvulsants, and so on. The most frequent are cyanotic and acyanotic congenital heart diseases. Acyanotic heart disease is distinguished by, among other things, a VSD, patent ductus arteriosus (PDA), arterial septal defect (ASD), and aortic stenosis (AS).[3] However, congenital heart disease has led the charts of most cardiac centers' data in recent years and proven to be the more common of the two. Many cases of congenital heart disease die during infancy, and in some children, the condition may not manifest until later in life, emphasizing the need of assessing the disease's prevalence.[4] The anomaly can be treated with medical therapy, surgery or device closure, or a heart transplant. Many children born with complex heart defects have reached maturity and are leading productive lives. Congenital heart disease is defined as a structural or functional heart illness that is present at birth, even if it is discovered later.[5] CHDs are the most common congenital malformations, accounting for around 8 cases per 1000 births.[6] If left untreated, a significant number of CHD patients with relevant systemic-to-pulmonary shunts will develop PAH. Eisenmenger syndrome is a congenital heart abnormality that results in a persistent, major left-to-right shunt, resulting in severe pulmonary vascular disease and PAH, followed by a bidirectional or reversed shunt, cyanosis, erythrocytosis, and organ involvement.[7,8] Patients with Eisenmenger syndrome have a poor quality of life, but the disease progresses slowly, as it does in most cases.[9] They live much longer than persons with idiopathic PAH and a functional class comparable.[10,11] The term pulmonary hypertension refers to elevated blood pressure in the pulmonary arterial tree. The term PAH refers to changes that affect the pulmonary vasculature directly, i.e., group 1 pulmonary hypertension, which is the primary focus of this study. The fundamental pathophysiology of this set of illnesses is thought to be similar: vasoconstriction, smooth muscle cell, endothelial proliferation, and intravascular thrombosis.[12] The diagnosis of pulmonary hypertension is usually delayed, necessitating a comprehensive evaluation to rule out other conditions and determine the likely cause. The vaso-reactivity test is critical for determining whether patients will benefit from calcium channel blockers.[13] Some facilities use cardiopulmonary exercise testing, which may be advantageous. Many indicators are widely used to track improvement after a PAH diagnosis. There are various general measures for PAH. To begin, it is recommended that where there is an associated cause, such as sickle cell anemia, that this condition be optimized. Lifestyle advice includes limiting activities to avoid symptoms, family planning advice, and preparation for surgery or anesthesia.[14,15] Oxygen therapy is advised in cases of hypoxemia. It should also be considered for persons flying, as decreased cabin pressure might cause dyspnea. Through dilatation and recruitment of underutilized vasculature, the pulmonary vascular bed can generally sustain increases in blood flow during exercise. This capacity is reduced in PHTN, resulting in higher pulmonary artery pressure. Dyspnea and syncope can occur when the heart is unable to raise its output in response to an increase in oxygen demand. Exertional and post-exertional syncopal episodes are more common in children, indicating a failure to adjust cardiac output and resulting in lower cerebral blood supply. The purpose of the present study was to understand and compare the side effects of monotherapy and combination therapy as a treatment method of PAH.

Objective

General objective

General objectives were to observe the side effects of monotherapy among patients, to observe the side effects of combination therapy among patients

Specific objectives

Specific objectives were to compare the side effects of monotherapy and combination therapy among both study groups.

METHODS

This randomized control trial study was conducted at the department of pediatric cardiology, Bangabandhu Sheikh Mujib medical university, national institute of cardiovascular disease, and national heart foundation, Dhaka, Bangladesh. The study duration was 1 year, from January 2018 to December 2018. During this time, 70 participants were chosen for the study based on inclusion and exclusion criteria from patients with pulmonary hypertension and congenital heart disease who were admitted to the pediatric cardiology department, Bangabandhu Sheikh Mujib medical university, NICVD, NHF. The chosen participants were then split into two groups of 35. The patients' outcomes were assessed using oxygen saturation (SPO_2) and a six-minute walking distance (6MWD). Patients in Group A received Sildenafil as monotherapy, whereas patients in Group B received both Sildenafil and Bosentan as combination therapy. Clinical data were examined. The total number of CHD cases, age, gender distribution, and type of CHD were all taken into account. The study group was first clinically evaluated using a predetermined proforma and then subjected to routine investigations such as a chest x-ray, electrocardiography, and echocardiography. Cardiac catheterization confirmed the final diagnosis. The clinical profile was then compared to the Cath results. For a minimum of six months, all patients were clinically evaluated once every three months and subjected to ECG, echocardiography, and the 6MWT. Patients' liver enzyme levels were measured every three months. To ensure confidentiality and anonymity, each patient was assigned a unique ID number, which was followed at every step of the procedure. After explaining the nature, objective,

procedure, risks, benefits, and implications of the study, the patient signed an informed consent form. 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. Statistical analyses were carried out by using the statistical package for social sciences version 23 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. The Chi-square test and unpaired t test were used for the analysis of qualitative, and quantitative variables respectively. P<0.05 was considered as a level of significance.

Inclusion criteria

Patients aged <18 years, patients with pulmonary hypertension, associated with congenital heart disease and patients who had given consent to participate in the study.

Exclusion criteria

Patients with idiopathic pulmonary hypertension, patients with persistent pulmonary hypertension of newborns, extremely morbid patients and patients unwilling to participate in the study were excluded from the study.

RESULTS

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 1).

Among the participants of both groups, 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-VSD, 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 2).

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 SpO_2 was 80.21% 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. SpO_2 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 2).

Table 1: Distribution of demographic characteristics in two groups, (n=70).

Demographic characteristics	Group A, (n=35)	Group B, (n=35)	P value
	N (%)	N (%)	
Age (Years)			
<8	4 (11.4)	6 (17.1)	
8-11	0 (0)	0 (0)	
12-15	19 (54.3)	21 (60)	0.105
16-18	12 (34.3)	8 (22.9)	
Age (Years) mean ± SD	16.4±3.97	14.81±4.12	
Gender			
Male	14 (40)	12 (34.3)	
Female	21 (60)	23 (65.7)	0.621
Male: female	01:01.5	01:01.9	
Socioeconomic status			
Lower middle	21 (60)	25 (68.6)	
Middle class	12 (34.3)	9 (25.7)	0.574
Upper class	2 (5.7)	1 (5.7)	

Data expressed as frequency, percentage, and mean ± SD

Unpaired student t test performed for quantitative variables and chi-square test used for qualitative variables

Figures in parentheses indicate corresponding percentage; Chi-squared test (χ^2) was done to analyze data.

Table 2: Type of congenital heart disease between two groups, (n=70).

Congenital heart disease	Group A, (n=35)	Group B, (n=35)	P value
	N (%)	N (%)	
ASD	5 (14.3)	6 (17.1)	
VSD	12 (34.3)	10 (28.6)	
Patent ductus arteriosus	4 (11.4)	3 (8.6)	
Aortopulmonary window	2 (5.7)	1 (2.9)	0.754
Aortic stenosis	1 (2.9)	0 (0)	
Single ventricle	2 (5.7)	4 (11.4)	
TAPVC with obstruction	2 (5.7)	2 (5.7)	
Atrio-VSD	7 (20)	9 (25.7)	
Total	35 (100)	35 (100)	

Table 3: Comparison of baseline clinical status, exercise tolerance, and biochemical parameters between two groups at baseline, (n=70).

Variables	Group A, (n=35), mean ± SD	Group B, (n=35), mean ± SD	P value
Clinical status			
SpO_2 (%) pre-exercise	80.21±9.2	82.12±8.3	0.481
Exercise tolerance (6MWT)			
Distance (m)	293.1±68.3	360.8±51.3	0.097
SpO_2 post-exercise (%)	63.2±15.2	72.6±10.7	0.081
Biochemical parameters			
Aspartate aminotransferase (U/l)	19.6±6.12	18.3±7.11	0.794
Alanine aminotransferase (U/l)	28.2±9.3	30.1±12.4	0.382

Data were expressed as mean ± SD, an unpaired student t-test was performed to compare between two groups.

Table 4: Comparison of clinical status, exercise tolerance, and biochemical parameters after 3 months between two groups, (n=70).

Variables	Group A, (n=35), mean ± SD	Group B, (n=35), mean ± SD	P value
Clinical status			
SpO_2 pre-exercise	78.6±8.1	84.13±9.23	0.002
Exercice tolerance (6MWT)			
Distance (m)	301.2±72.1	372.4±82.3	0.002
SpO_2 post-exercice (%)	64.13±14.6	74.12±11.1	0.034
Biochemical parameters			
Aspartate amino-transferase (U/l)	19.13±61	18.6±7.1	0.587
Alanine amino-transferase (U/l)	28.36±9.2	32.14±12.6	0.024

At the 3-month follow-up after the start of treatment, the study observed that mean SpO_2 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 SpO_2 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.

Table 5: Comparison of clinical status, exercise tolerance, and biochemical parameters after 6 months between two groups, (n=70).

Variables	Group A, (n=35), mean ± SD	Group B, (n=35), mean ± SD	P value
Clinical status			
SpO_2 (%) pre-exercise	80.2±8.3	86.28±8.54	0.041
Exercice tolerance (6MWT)			
Distance (m)	311.2±78.0	381.5±83.8	0.002
SpO_2 post-exercise (%)	66.4±13.8	77.21±12.3	0.034
Biochemical parameters			
Aspartate amino-transferase (U/l)	20.21±6.2	21.12±8.3	0.854
Alanine amino-transferase (U/l)	32.37±9.1	35.8±13.8	0.339

At the 6-month follow-up after the start of treatment, SpO_2 pre-exercise, 6MWT distance, and SpO_2 post-exercise had all been significantly higher among group-B participants.

Table 6: Association of adverse effects in two groups, (n=70).

Adverse effects	Group A, (n=35)	Group B, (n=35)	P value
	N (%)	N (%)	
Upper respiratory tract infection	26 (74.3)	22 (62.9)	0.307
Vomiting	33 (94.3)	30 (85.7)	0.235
Headache	27 (77.1)	30 (85.7)	0.360
Bronchitis	11 (31.4)	13 (37.1)	0.617
Pyrexia	5 (14.3)	7 (20)	0.528
Pharyngitis	3 (8.6)	5 (14.3)	0.456
Cough	6 (17.1)	8 (22.9)	0.553
Diarrhea	3 (8.6)	4 (11.4)	0.692
Nasopharyngitis	2 (5.7)	1 (2.9)	0.558

The adverse effects of both groups were recorded in study, and no significant association observed between 2 groups. However, upper respiratory tract infection and vomiting had a higher prevalence in group A participants.

DISCUSSION

During the study period, 70 patients were enrolled: 35 were assigned to sildenafil monotherapy (Group A), and

35 to sildenafil and Bosentan combination therapy (Group B) (Group B). The majority of patients were between the ages of 12 and 15, with 54.3% in group A and 60% in group B. Group A (Sildenafil group) included 35 patients, 14 (40%) of whom were males and 21 (21%) of whom were females (60%). In group B (combination group), 12 (34.4%) of the patients were male, while 23 (65.7%) were female. Due to the randomized selection of participants in the groups, no significant difference in sociological characteristics was observed between the groups. The most common congenital heart anomaly among both groups' participants was a VSD. VSD was present in 34.3% of group A and 28.6% of group B, followed by AVSD (20% in group A and 25.7% in group B) and ASD (14.3% in group A, and 17.1% in group B). The randomization of group selection resulted in no significant differences between the groups. After three and six months of follow-up, the distance of exercise tolerance (6MWD), SpO_2 post-exercise, and alanine aminotransferase were statistically different between the single (Group A) and combined (Group B) groups for clinical variables, exercise tolerance, and biochemical parameters. These findings outperformed those of Durongpisitkul et al who discovered that half of their study participants experienced clinical worsening within 12 months of starting treatment.[16] Patients who received initial Bosentan monotherapy were significantly less likely to experience clinical worsening than sildenafil and Bosentan recipients at 12 months (16.7% vs. 38.3%, and 71.4%, respectively; p=0.039), and 24 months (16.7% vs. 61.7%, and 77.1%, respectively; p=0.007). Thirty-three patients who had failed initial monotherapy were given sequential combination therapy. The 6MWD (mean ± standard error) increased significantly after the commencement of sequential combination therapy from 208.9±67.2 m before the addition of the second drug to 285.5±92.1 m at 1 month (p=0.09), and 326.3±62.7 m at 3 months (p=0.001), which was consistent with present study findings. These findings suggest that patients receiving sildenafil monotherapy were significantly more likely to experience clinical worsening at 3 and 6 months compared to sildenafil and Bosentan recipients. A retrospective analytical study yielded comparable results.[17] However, a study with Eisenmenger syndrome patients found that upfront combination therapy with Bosentan and sildenafil was not superior to Bosentan monotherapy in terms of changes in 6MWD.[18] As a result, the general treatment approach is to observe and record clinical worsening in order to guide the decision to escalate treatment only when necessary. A goal-oriented treatment strategy based on predictors of improved survival has been demonstrated to be an important strategy for managing PAH patients.[19,20] The better efficiency results in our study compared to Iversen et al were most likely due to the fact that our study first evaluated the effects of add-on sildenafil therapy in CHD-related PAH patients who showed clinical worsening after oral Bosentan. Both the 3-month and 6-month follow-ups revealed clinical improvement in our population. A significant increase in SpO_2 was also observed at the end of the 6MWT, which was likely due to the drugs' stronger effect on the pulmonary rather than systemic circulation, and, in general, to the patients' better hemodynamic profile. The most common side effects of sildenafil and Bosentan treatment are usually non-fatal. Upper respiratory tract infections were the most common adverse reaction to the treatment, followed by vomiting, headache, bronchitis, pyrexia, pharyngitis, cough, diarrhea, and nasopharyngitis in that order. In the current study, there were no statistically significant differences between the two groups in terms of adverse effects. It was discovered that patients receiving monotherapy had a slightly higher incidence rate of upper respiratory tract infection and vomiting, whereas patients receiving combination therapy had a slightly higher incidence rate of headache, bronchitis, pyrexia, pharyngitis, cough, and diarrhea.

Limitations

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

CONCLUSION

This study concludes that combination therapy is more successful than monotherapy in PAH with CHD. Our findings demonstrate that combining Bosentan with oral Sildenafil medication in patients with CHD-related PAH is safe, and well tolerated at 3-, and 6-month follow-ups, resulting in a significant improvement in clinical status, effort SpO_2, exercise tolerance, hemodynamics, and PASP.

Recommendations

Further research is needed to conclude the ideal posology of Sildenafil and to establish its place in future developments, and therapies in the field of pediatric cardiology. Careful patient management is recommended in the current monitoring schedule and flow-chart for modifying the dosing schedule in case of elevated liver function tests or significant side effects.

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