International Journal of Research in Medical Sciences
Anam AN et al. Int J Res Med Sci. 2023 Jan;11(1):10-15
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20223295

Original Research Article

Comparison of short-term outcome between monotherapy versus combination therapy in the treatment of pulmonary hypertension associated with congenital heart disease

Ahmed Nazmul Anam*, Nazmul Hossain, Hasrat Jahan, Bidhan Chandra Podder, Monzurul Karim

Department of Pediatrics, Institute of Child and Mother Health, Dhaka, Bangladesh

Received: 16 November 2022
Revised: 04 December 2022
Accepted: 05 December 2022

***Correspondence:**
Dr. Ahmed Nazmul Anam,
E-mail: kariul@hotmail.com

ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a severe condition marked by a progressive rise in pulmonary vascular resistance (PVR), which leads to right heart failure, and mortality. Combining medications is an appealing approach for treating PAH patients. The current study sought to compare the outcomes of monotherapy, and combination therapy after a short period of follow-up. 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 pediatric cardiology, Bangabandhu Sheikh Mujib medical university, national institute of cardiovascular disease, and national heart foundation, Dhaka, Bangladesh, 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. The selected participants were then divided into two groups of 35 each through random selection.
Result: There were no significant differences between the two groups in terms of mean age, and sex. The 34.3% in Group A, and 28.6% in group B had ventricular septal defects (VSD, followed by AVSD at 20.0% in group A and 25.7% in Group B. After 3 and 6 months of follow-up SpO_2 per exercise, 6MWD, SpO2 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 two groups. PASP was significantly decreased in the combined group than monotherapy group.
Conclusions: Combination therapy is more successful than monotherapy in PAH with CHD. Combining bosentan with oral sildenafil medication in patients with CHD-related PAH is safe, and well tolerated at follow-ups.

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

INTRODUCTION

Congenital heart disease (CHD) is the most prevalent birth defect, accounting for over 30% of all congenital malformations. During development, the heart develops from a rudimentary muscle wrapping to a four-chambered muscular organ with septa, valves, a conduction system, and major arteries beginning, and terminating in the heart. Any flaw in the development's orderly, and sequential progression results in structural or functional abnormality.[1] During intrauterine life, the lungs receive 10% of the cardiac output. The remaining 90% is sent to the aorta, and systemic circulation via the patent ductus arteriosus (PDA). To ensure normal gas exchange, the majority of the right ventricular output should flow via the lungs after birth. To accomplish this, ductus constriction, and functional closure occur shortly

after birth in term newborns. In term newborns, the ductus arteriosus closes in 48 hours, and nearly completely in 96 hours. Failure of this normal closure causes complications, particularly in pre-term infants.[2,3] The exact etiology of CHD is unknown, however, numerous factors are linked to it, including parental viral infection, poor maternal nutritional status, mother's age over 40, insulin-dependent diabetes, and usage of medicines such as lithium, anticonvulsants, and so on. Acyanotic and cyanotic congenital cardiac disorders are the most common. Acyanotic heart disease is characterized by a VSD, PDA, arterial septal defect (ASD), and aortic stenosis (AS), among other conditions. However, in recent years, CHD has topped the charts of most cardiac centers' data and proven to be the more common of the two. Many cases of CHD die during infancy, and in some children, the ailment does not emerge until later in life, highlighting the importance of determining the prevalence of this disease.[4] Medical therapy, surgery or device closure, and heart transplant are all options for treating the abnormality. Many children born with complicated heart abnormalities now reach adulthood and live productive lives. CHD 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 prevalent congenital defects, accounting for around 8 occurrences per 1000 newborns.[6] If left untreated, a considerable proportion of individuals with CHD who have relevant systemic-to-pulmonary shunts will develop PAH. Eisenmenger syndrome is a congenital cardiac defect that creates a chronic, massive left-to-right shunt that causes severe pulmonary vascular disease, and PAH, followed by a bidirectional or reversed shunt, cyanosis, erythrocytosis, and various organ involvement.[7,8] Eisenmenger patients have a bad quality of life, but the disease advances slowly, as it does in most cases.[9] They live significantly longer than people with idiopathic PAH, and an equivalent functional class.[10,11] Pulmonary hypertension is an umbrella term for high blood pressure in the pulmonary arterial tree. The term PAH refers to alterations that directly affect the pulmonary vasculature, i.e., group 1 pulmonary hypertension, which is the primary focus of this research. This group of disorders appears different, but the underlying pathophysiology is assumed to be similar: vasoconstriction, smooth muscle cell, endothelial growth, and intravascular thrombosis.[12] The diagnosis of pulmonary hypertension is frequently delayed, and necessitates a thorough examination to rule out other illnesses, and identify the likely cause of pulmonary hypertension. The vaso-reactivity test is essential for identifying people who will benefit from calcium channel blockers.[13,14] Cardiopulmonary exercise testing is utilized at some facilities and may be beneficial. Following a PAH diagnosis, many measures are commonly performed to track improvement. For PAH, several general measures are indicated. To begin, where there is an associated cause, such as sickle cell anemia, it is recommended that this condition be optimized. Limiting activity to avoid symptoms, family planning guidance, and planning if surgery or anesthesia are required are all examples of lifestyle advice.[15] In the event of hypoxemia, oxygen therapy is recommended. It should also be considered for people traveling by plane, as the low cabin pressure may cause dyspnea. The pulmonary vascular bed can normally tolerate increases in blood flow during exercise through dilatation, and recruitment of underused vasculature. With PHTN, this capacity is decreased, resulting in increased pulmonary artery pressure. Dyspnea and syncope can result from an inability to increase cardiac output in response to increases in oxygen demand. Exertional, and postexertional syncopal episodes are more common in youngsters, indicating a lack of cardiac output correction, and resulting in decreased cerebral blood flow. The study's goal is to compare the efficacy of sildenafil monotherapy with combination therapy with bosentan (Sildenafil + bosentan) in the treatment of pulmonary hypertension in children with CHD.

Objective

General objective

General objective were to observe the short-term outcome of monotherapy with sildenafil in patients with pulmonary hypertension and to observe the short-term outcome of combination therapy with sildenafil and bosentan in patients with pulmonary hypertension.

Specific objectives

Specific objectives were 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 pediatric cardiology, Bangabandhu Sheikh Mujib medical university, national institute of cardiovascular disease, and national heart foundation, Dhaka, Bangladesh. The study duration was 1 year, fro 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 CHD admitted to the pediatric cardiology department, Bangabandhu Sheikh Mujib medical university, NICVD, NHF. Inclusion criteria for the patients was patients aged <18 years who had pulmonary Hypertension, associated with CHD. Patients with idiopathic pulmonary hypertension, persistent pulmonary hypertension of newborns and extremely morbid patients were excluded from the study. The selected participants were then divided into two groups of 35 each. Outcomes of the patients were measured using saturation of oxygen (SPO_2), and a six-minute walking distance (6MWD). Patients of group A had received Sildenafil as monotherapy treatment, while group-B patients had

received both sildenafil and bosentan as combination therapy. Clinical data were reviewed. Consideration was given to the total number of cases with CHD, age, sex distribution, and type of CHD. The study group was first assessed clinically according to a preformed proforma and underwent routine investigations, chest x-ray, electrocardiography, and echocardiography. The final diagnosis was confirmed by cardiac catheterization. The clinical profile was then correlated with cath findings. All patients were clinically evaluated once every three months for a minimum of six months; all were investigated by ECG, echocardiography, and the 6MWT. Liver enzyme levels were measured every three months in patients. For safeguarding confidentiality, and protecting anonymity, each of the patients was given a special ID number which was followed at each, and every step of the procedure. A signed informed consent was taken from the patient after explaining to them 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. Statistical analyses were carried out by using the statistical package for social sciences version 23.0 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 CHD and patients who had given consent to participate in the study were included.

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: 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)	0.105
8-11	0 (0)	0 (0)	
12-15	19 (54.3)	21 (60	
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)	0.621
Female	21 (60)	23 (65.7)	
Male: female ratio	01:01.5	01:01.9	
Socioeconomic status			
Lower middle class	21 (60)	25 (68.6)	0.574
Middle class	12 (34.3)	9 (25.7)	
Upper class	2 (5.7%)	1 (5.7%)	

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.

Table 2: Type of CHD between two groups, (n=70).

CHD	Group A, (n=35)	Group B, (n=35)	P value
	No (%)	N (%)	
Atrial septal defect (ASD)	5 (14.3)	6 (17.1)	0.754
VSD	12 (34.3)	10 (28.6)	
PDA	4 (11.4)	3 (8.6)	
Aortopulmonary window	2 (5.7)	1 (2.9)	
AS	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)	

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, 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 CHD s 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=70).

Variables	Group A, (n=35)	Group B, (n=35)	P value
	Mean ± SD	Mean ± SD	
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.

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.

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.

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

Variables	Group A, (n=35)	Group B, (n=35)	P value
	Mean ± SD	Mean ± SD	
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-exercise (%)	64.13±14.6	74.12±11.1	0.034
Biochemical parameters			
Aspartate aminotransferase (U/l)	19.13±61	18.6±7.1	0.587 ns
Alanine aminotransferase (U/l)	28.36±9.2	32.14±12.6	0.024*

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

Variables	Group A, (n=35)	Group B, (n=35)	P value
	Mean ± SD	Mean ± SD	
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 aminotransferase (U/l)	20.21±6.2	21.12±8.3	0.854
Alanine aminotransferase (U/l)	32.37±9.1	35.8±13.8	0.339

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

Adverse effects	Group A, (n=35)	Group B, (n=35)	P value
	No. (%)	No. (%)	
URT 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)	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 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 7: Association of echocardiographic findings between groups, (n=70).

Echo-cardiographic findings (PASP)	Group A, (n=35)		Group B, (n=35)		P value
	N	%	N	%	
Mild	10	28.60	23	65.70	0
Moderate	11	31.40	9	25.70	
Severe	14	40	3	8.60	
Mean ± SD	56.15±11.24		38.35±10.12		

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 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.

DISCUSSION

During the study period, 70 patients were enrolled: 35 were randomized to Sildenafil monotherapy (Group A), and 35 to the combination treatment of sildenafil, and bosentan (Group B). Maximum patients were in the age group 12-15 years, 54.3% in group A, and 60.0% in group B. Group A (Sildenafil group) consisted of 35 patients, 14 (40.0%) males, and 21 females (60.0%). In group B (combination group) 12 (34.4%) patients were male, and 23 (65.7%) patients were female. Due to the randomized selection of the participants in the groups, no significant difference was observed between the groups in regard to sociological characteristics. VSD was the most common congenital heart anomaly between participants of both groups. 34.3% in group A and 28.6% in group B had VSD, 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). No significant difference was observed between the groups due to the randomization of group selection. In this trial regarding clinical variables, exercise tolerance, and biochemical parameters, after three, and 6 months of follow-up of SpO_2 pre-exercise, the distance of exercise tolerance (6MWD), SpO_2 post-exercise, and alanine aminotransferase were statistically different between single (Group-A), and combined (Group-B) group. These findings were better than the findings of Durongpisitkul et al who observed 50% of their study participants having a clinical worsening within 12 months of commencing treatment.[16] In their study, Patients who received initial bosentan monotherapy were significantly less likely to experience clinical worsening compared with 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 failed initial monotherapy were subsequently prescribed 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 is consistent with present study findings. These findings suggest that patients receiving Sildenafil monotherapy were significantly more likely to experience clinical worsening compared with sildenafil, and Bosentan recipients at 3 months, and 6 months. A retrospective analytical study also showed similar results.[17] However, a study with patients suffering from Eisenmenger syndrome showed that upfront combination therapy with bosentan and sildenafil was not superior to bosentan monotherapy concerning changes in 6MWD.[18] As such, the general approach regarding treatment is to observe and record clinical worsening, to guide the decision to escalate treatment only when necessary. A goal-oriented treatment approach based on predictors of improved survival has been shown to be an important strategy for managing patients with PAH.[19,20] The better results in terms of efficiency in our study compared to that of Iversen et al.'s were probably because our study first evaluated the effects of add-on sildenafil therapy in CHD-related PAH patients showing clinical worsening after oral bosentan. Clinical improvement was observed in our population at both the 3-month, and 6-month follow-up. A significant increase in SpO_2 at the end of 6MWT was also observed which was likely due to the stronger effect of the drugs used on the pulmonary, rather than the systemic circulation, and, in general, to a better hemodynamic profile of the patients. Common side effects of Sildenafil and Bosentan treatment are usually non-life-threatening. Upper respiratory tract infections were the most frequent of the adverse reactions to the treatment, followed, in order of frequency, by vomiting, headache, bronchitis, pyrexia, pharyngitis, cough, diarrhea, and nasopharyngitis. In the present study regarding adverse effects, there were no statistically significant differences between the two groups. The use of Sildenafil, and Bosentan in the treatment of PAH in infants, and children has shown potential benefits and improved patient outcomes. Analysis indicates that there was a significant difference in echocardiographic findings between the two groups regarding PASP. PASP significantly decreased in the combined group compared to the monotherapy group. These findings were supported by the findings of Pan et al.[21]

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 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.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Parthasorathy A, Nair MKC, Menon PSN. IAP Textbook of Paediatrics Nursing. 3rd ed. New Delhi: Jaypee Publishers. 2006.
2. Aggarwal R, Bajpai A, Deorari KA, Paul KV. Patent Ductus Arteriosus in Preterm Neonates. IJP. 2001;68:981-4.
3. Tambulwalkar RS. Paediatric Nursing. 2nd ed. Mumbai: Vora Medical Publication. 2001;1.
4. Chadha SL, Neerpal S, Shukla DK. Epidemiology Study of Congenital Heart Disease. Ind J Paediatr. 2001;68(6):507.
5. Rahim F, Younas M, Gandapur AJ, Talat A. Pattern of congenital heart disease in a tertiary care center, Peshawar. Pak J Med Sci. 2003;19(1):19-22.
6. Hoffmann JL, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890-900.
7. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J. 1958;2:755-62.
8. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA et al. Guidelines for the diagnosis, and treatment of pulmonary hypertension. The Task Force for the Diagnosis, and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC), and the European Respiratory Society (ERS), endorsed by the International Society of Heart, and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493-537.
9. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA. Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension, and management implications. Curr Opin Cardiol. 2008;23:545-54.
10. Beghetti M, Galie N. Eisenmenger syndrome: a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;53:733-40.
11. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective, and case–control study. Eur Heart J. 2006;27:1737-42.
12. Farber HW, Loscalzo J. Mechanisms of disease: pulmonary hypertension. New Engl J Med. 2004;351:1655-65.
13. Barst R, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H et al. Diagnosis, and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43:S40-7.
14. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104:429-35.
15. Galie N, Torbicki A, Barst R. Guidelines on diagnosis, and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis, and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004;25:2243-78.
16. Durongpisitkul K, Plearntammakun P, Vijarsorn C. A Retrospective Evaluation of Pulmonary Vasodilator Monotherapy, and Sequential Combination Therapy in Thai Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease. J Cardiovasc Res. 2016;5(4):1-5.
17. Monfredi O, Heward E, Griffiths L, Condliffe R, Mahadevan VS. Effect of dual pulmonary vasodilator therapy in pulmonary arterial hypertension associated with congenital heart disease: a retrospective analysis. Open heart. 2016;3(1):e000399.
18. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Søndergaard L. Combination therapy with bosentan, and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur heart J. 2010;31(9):1124-31.
19. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respiratory J. 2012;39(3):589-96.
20. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment, and combination therapy for pulmonary arterial hypertension. Eur Respiratory J. 2005;26(5):858-63.
21. Pan J, Lei L, Zhao C. Comparison between the efficacy of combination therapy, and monotherapy in connective tissue disease associated pulmonary arterial hypertension: a systematic review, and meta-analysis. Clin Expe Rheumatol. 2018;36(6):1095-102.

Cite this article as: Anam AN, Hossain N, Jahan H, Podder BC, Karim M. Comparison of short-term outcome between monotherapy versus combination therapy in the treatment of pulmonary hypertension associated with congenital heart disease. Int J Res Med Sci 2023;11:10-5.