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ORIGINAL ARTICLE

Comparative Study of Ambrisentan and Sildenafil on Surgical Outcome in Left to Right Shunt Anomaly Patients with Pulmonary Hypertension

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Abstract:

Background: *Pulmonary hypertension is common in patients with atrial septal defect, ventricular septal defect and patent ductus arteriosus. Closure of large left to right cardiac shunts with preexisting significant pulmonary arterial hypertension is usually accompanied by hazards of post-operative residual pulmonary arterial hypertension, pulmonary hypertensive crisis and right ventricular dysfunction. Pulmonary vasodilator drugs should be used in left to right shunt anomaly patients with pulmonary hypertension for reduction of pulmonary hypertension and should be continued postoperatively for better surgical outcome. This study compares short term surgical outcome of left to right shunt anomaly patients with pulmonary hypertension between preoperative and postoperative therapy with ambrisentan and sildenafil.*

Methods: *The study was conducted in the department of cardiac surgery of Bangabandhu Sheikh Mujib Medical University and National Institute of Cardiovascular Diseases (*NICVD*) from February 2014 to February 2016 in left to right shunt atrial septal defect or ventricular septal defect or patent ductus arteriosus patients with moderate to severe pulmonary hypertension. Among 40 patients; 20 patients of group-1 recei-ved ambrisentan and another 20 patients of group-2 received sildenafil during pre-operative and postoperative period up to 3 months. Colour Doppler echocardiography was used to measure pulmonary artery systolic pressure in both groups except per operative pulmonary artery systolic pressure which was measured directly by pulmo-nary arterial line. Recorded pulmonary artery systolic pressure, cardiopulmonary by-pass time, duration of mechanical ventilation time and death were compared between two groups. Data were presented as Mean ± SD. Differences between two groups were compared using chi-square and* t *test. P value less than 0.05 was considered to be significant.*

Results: *The mean difference of pulmonary artery systolic pressure after admission and 15 days after starting medication were statistically not significant between two groups ($p > 0.05$). Reduction of pulmonary artery systolic pressure after correction (Post by-pass) were occurred in both groups. But the mean difference of pulmonary artery sys-tolic pressure after correction (Post bypass) was statistically not significant beween the two groups ($p > 0.05$). Ambrisentan group showed more reduction of pulmonary artery systolic pressure postoperatively than sildenafil group. Postoperatively signi-ficant shortened cardiopulmonary bypass time and mechanical ventilation time was found in ambrisentan group in comparison to sildenafil group.*

Conclusions: *Ambrisentan has better surgical outcome than sildenafil in left to right shunt ano-maly patients with moderate to severe pulmonary hypertension.*

Key words: *Ambrisentan, Left to right shunt anomaly, Pulmonary hypertension, Sildenafil.*

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Introduction:

Pulmonary hypertension is common in patients with adult congenital heart disease (about 10%). Congenital heart defects leading to pulmonary hypertension can be simple (atrial septal defect, ventricular septal defect, patent ductus arteriosus) or complex (atrioventricular septal defect, truncus arteriosus).[1] It has been possible to reduce pulmonary vascular resistance because of improvement in pulmonary vaso-dilators and more widespread use of pulmonary vasodilators. Then patient with pulmonary arterial hypertension are amenable to surgery.[2] Recent advances in pedi-atric cardiac surgery techniques have increased ability to correct congenital heart disease at an early age.[3]

The pathogenesis of pulmonary hypertension (PH) is complex and multifactorial. Increased pulmonary arterial pressure (PAP) in patients with pulmonary hypertension probably results from combination of pulmonary vasoconstriction, inward vascular wall remodelling and in situ thrombosis.[4]

Affinity of ambrisentan for ETA receptor is >4000-fold than affinity for ETB recep-tor. Administration of ambrisentan in patients with pulmonary arterial hypertension is associated with vascular smooth muscle relaxation and vasodilatation. Bosentan, another ET-1 receptor antagonist, has 100 times greater affinity for ETA receptor than for ETB receptor. So, ambrisentan is more specific ETA-receptor antagonist than bosentan.[5]

"Food and Drug Administration" approved ambrisentan in June 2007.[4] (Wal et al., 2013). Ambrisentan was approved in United States in 2007. Ambrisentan was later approved for use in Canada (In 2008), Europian Union (In 2008), New Zealand (In 20109), Australia (In 2009) and Japan (In 2010).[6] The current approved dose of ambrisentan is 5 mg once daily which can be increased to 10 mg once daily when the drug is tolerated at the initial dose.[7] In the clinical setting, pediatric patients can be started on ambrisentan at the initial 2.5 (<20 kg) or 5 mg dose (>_20 kg) and considered for an up-titration to the 5–10 mg dose.[8] Dose of ambrisentan incase of adult over 18 years is 5 mg once daily and can be increased to 10 mg once daily if necessary.[9] Ambrisentan is highly bound to plasma proteins (99%). Elimination is mostly through biliary system with majority of oral doses recovered in urine and feces. Ambrisentan half life ranges from 13.6 to 16.5 hours.[10]

Sildenafil has been used to treat pulmonary hypertension in both pediatric and adult patients that have undergone cardiac surgery.[11] Sildenafil increases effects of locally produced nitric oxide (NO) by inhibiting break-down of cyclic guanosine mono-phosphate. This results in pulmonary vasodilation and inhibition of smooth muscle cell growth.[12] Dose of of sildenafil is 20 mg 3 times daily.[9] Sildenafil was approved by European Medicines in 2011. Dose of sildenafil is 10 mg 3 times daily for weight less than 20 kg and 20 mg 3 times daily for weight equal and more than 20 kg.[13] Half-life of sildenafil is approximately 4 hours and bioavailability is approximately 40% which is reduced to 29% following a large meal.[14] The most serious adverse effects of sildenafil are arrhythmias, heart block, cardiac arrest, stroke and hypotension.[15]

Closure of large left to right cardiac shunts with preexisting significant pulmonary ar-terial hypertension is usually accompanied by hazards of post-operative residual pulmonary arterial hypertension, pulmonary hypertensive crisis and right ventricular dysfunction.[16] The goal of perioperative pulmonary arterial hypertension therapy is to maximize pulmonary vasodilatation and reduce pulmonary vascular resistance. This decreases right ventricular afterload and subsequently improves cardiac output.[11]

Pulmonary vasodilator drugs should be used in left to right shunt anomaly patients with pulmonary hypertension for reduction of pulmonary hypertension and should be continued postoperatively for better surgical outcome. It should be known which pulmonary vasodilator drug has better surgical outcome in left to right shunt anomaly patients with pulmonary hypertension. The aim of this study is to compare short term surgical outcome of left to right shunt anomaly patients with pulmonary hypertension between preoperative and postoperative therapy with ambrisentan and sildenafil.

Materials and methods:

This clinical observational study was conducted in the department of cardiac surgery of Bangabandhu Sheikh Mujib Medical University and National Institute of Cardio-vascular Diseases (*NICVD*) from February 2014 to February 2016 in left to right shunt atrial septal defect or ventricular septal defect or patent ductus arteriosus patients with pulmonary

arterial systolic pressure 50 to 100 mm Hg. The per-mission from the institutional review board of Bangabandhu Sheikh Mujib Medi-cal University (BSMMU) and informed consent from all patients were obtained for this study. Among 40 patients; 20 patients of group-1 received ambrisentan and another 20 patients of group-2 received sildenafil during preoperative and post-operative period.

Preoperatively ambrisentan was given to group-1 patients via oral route at a dose of 2.5 mg in <20 kg case and 5 mg in >_20 kg case once daily. Sildenafil was given to group-2 patients via oral route 25 mg 3 times daily in adult or 0.5 mg/ kg in pedi-atric case in every 8 hourly for 15 days with the final dose 8 hours before induction of anaesthesia. Postoperatively patients of group-1 were got ambrisentan and patients of group- 2 were got sildenafil from the day of operation in intensive care unit via nasogastric tube till extubation and then via oral route after extubation up to 3 months postoperatively.

Pulmonary artery systolic pressure were measured after admission, 15 days after starting medication, before correction (Prebypass), after correction(Post bypass), at 7th post-operative day, at 1 month after operation and at 3 month after operation in both groups.

Colour Doppler echocardiography was used to measure pulmonary artery systolic pressure in both groups except per operative pulmonary artery systolic pressure. Per operative pulmonary artery systolic pressure was measured directly by pulmonary arterial line. Recorded pulmonary artery systolic pressure, cardiopulmonary bypass time, duration of mechanical ventilation time and death were compared between two groups. Data were presented as Mean ± SD. Differences between two groups were compared using chi-square and Student's t-test. P value less than 0.05 was considered to be significant.

Results:

Total number of 40 (Forty) patients were selected for the study. There were two groups; group-1 and group -2. Among 40 patients; 20 patients were in group-1 and 20 patients were in group-2. All patients of group-1 received ambrisentan and all patients of group-2 received sildenafil during preoperative and postoperative period. The findings of the study obtained from data analysis are presented below.

Age distribution of the selected patients between group-1 and group-2 are showed in table-I. The mean age in group-1 was 24.85±13.98 and in group-2 was 20.8±12.19. It was observed that mean age was not significantly different bet-ween two groups (p> 0.05).

Table-I

Comparison of age between two groups

Variable	Group 1 (n=20)	Group 2 (n=20)	P value
Age	Mean±SD 24.85±13.98	Mean±SD 20.8±12.19	0.33 ^{ns}

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Sex distribution of the selected patients between group-1 and group-2 are showed in table-II. It was found that 20% were male and 80% were female in group-1. In group-2, 25% were male and 75 % were female. There was no significant difference in sex distribution between two groups (p> 0.05).

Weight distribution of the selected patients between group-1 and group-2 are showed in table-III. Mean weight in group-1 was 40.8±15.55 and in group-2 was 38.25±16.03. It was observed that mean weight was not significantly different between two groups (p> 0.05).

Table-II

Comparison of sex between two groups

Sex	Group-1(n=20)		Group-2(n=20)		P value
	Number	Percentage	Number	Percentage	
Male	4	20%	5	25%	0.70^{ns}
Female	16	80%	15	75%	
Total	20	100%	20	100%	

Data were expressed as number and percentage.
Statistical analysis were done by Chi-square test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Table-III

Comparison of weight between two groups

Variable	Group 1 (n=20)	Group 2 (n=20)	P value
Weight(Kg)	Mean±SD 40.8±15.55	Mean±SD 38.25±16.03	0.61 ns

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Type of operation performed between two groups are shown in table-IV. In group-1 80% ASD (Atrial septal defect) closure , 15% VSD (Ventricular septal defect) closure and 5% PDA(Patent ductus arteriosus) ligation were done. In group-2 75% ASD (Atrial septal defect) closure , 20 % VSD (Ventricular septal defect) closure and 5% PDA(Patent ductus arteriosus) ligation were done. There was no significant difference in type of operation performed between two groups (p> 0.05).

Table-IV

Comparison of type of operation performed between two groups

Variable	Group-1 N=20		Group-2 N=20		P value
	Number	%	Number	%	
ASD	16	80%	15	75%	0.92 ns
VSD	3	15%	4	20%	
PDA	1	5%	1	5%	
Total	20	100%	20	100%	

Data were expressed as number and percentage.
Statistical analysis were done by Chi-square test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Table-V shows pulmonary artery systolic pressure after admission in two groups. Mean pulmonary artery systolic pressure after admission in group-1 was 68.45 ± 11.57 and 68.95±11.01 in group-2. The mean difference of pulmonary artery systolic pressure after admission was statistically not significant between the two groups (p > 0.05).

Table-V

Comparison of Pulmonary artery systolic pressure after admission between two groups:

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure after admission	Mean ± SD 68.45 ± 11.57	Mean±SD 68.95±11.01	0.89 ns

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Table-VI compares pulmonary artery systolic pressure 15 days after starting medi-cation between two groups. Mean pulmonary artery systolic pressure 15 days after starting medication in group-1 was 60.7±10.91 and in group-2 was 63.3±9.88. Reduction of pulmonary artery systolic pressure 15 days after starting medication were occurred in both group. But the mean difference of pulmonary artery systolic pressure 15 days after starting medication was statistically not significant between the two groups (p > 0.05).

Table-VI

Comparison of pulmonary artery systolic pressure 15 days after starting medication between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure 15 days after starting medication	Mean±SD 60.7± 10.91	Mean±SD 63.3±9.88	0.43 ns

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Pulmonary artery systolic pressure before correction (Pre bypass) between two groups are shown in table-VII. Mean pulmonary artery systolic pressure before correction (Pre bypass) in group-1 was 57.35±10.08 and 59.65±8.64 in group-2. The mean difference of pulmonary artery systolic pressure before correction (Pre bypass) was statistically not significant between the two groups (p > 0.05).

Table-VII

Comparison of Pulmonary artery systolic pressure before correction (Pre bypass) between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure before correction (Pre bypass)	Mean±SD 57.35±10.08	Mean±SD 59.65±8.64	0.44 ns

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n=number of subjects; ns= Not significant.

Table-VIII compares pulmonary artery systolic pressure after correction (Post bypass) between two groups. Mean pulmonary artery systolic pressure after correc-tion (Post bypass) in group-1 was 45.35± 9.06 and in group-2 was 50 ±7.87. Reduction of pulmonary artery systolic pressure after correction(Post bypass) were occurred in both groups. But the mean difference of pulmonary artery systolic pre-ssure after correction (Post bypass) was statistically not significant between the two groups ($p > 0.05$).

Table-VIII

Comparison of pulmonary artery systolic pressure after correction (Post bypass) between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure after correction (Post bypass)	Mean±SD 45.35± 9.06	Mean±SD 50 ±7.87	0.09 ns

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test.
Level of significance was $p< 0.05$.
n=number of subjects; ns= Not significant.

Comparison of pulmonary artery systolic pressure at 7th post operative day bet-ween two groups are shown in table-IX. Mean pulmonary artery systolic pressure at 7th post operative day in group-1 was 41.35± 8.61 and in group-2 was 46.65 ±7.67. It was observed that mean pulmonary artery systolic pressure at 7th post operative day was significantly different between two groups ($p< 0.05$).

Table-IX

Comparison of Pulmonary artery systolic pressure at 7th post operative day between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure at 7th post ope-rative day	Mean±SD 41.35± 8.61	Mean±SD 46.65±7.67	0.04 s

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was $p< 0.05$.
n = number of subjects; s = significant

Table-X shows pulmonary artery systolic pressure at 1 month after operation in two groups. Mean pulmonary artery systolic pressure at 1 month after operation in group-1 was 34.35 ±7.35 and 39.75 ± 6.79 in group-2. Statistically significant difference was present in between two groups ($p < 0.05$).

Table-X

Comparison of Pulmonary artery systolic pressure at 1 month after operation between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure at 1 month after operation	Mean±SD 34.35 ±7.35	Mean±SD 39.75±6.79	0.02 s

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was $p< 0.05$.
n = number of subjects; s = significant

Table-XI shows pulmonary artery systolic pressure at 3 month after operation in two study groups. Mean pulmonary artery systolic pressure at 3 month after opera-tion in group-1 was 23.9 ± 4.91 and in group-2 was 27.9 ± 5.16. The difference of pulmonary artery systolic pressure at 3 month after operation between two groups was statistically significant ($p < 0.05$).

Table-XII shows cardiopulmonary bypass time between two groups. The mean car-diopulmonary bypass time in group-1 was 76.74±20.97 and in group-2 was 93.16 ±27.18. The mean difference of cardiopulmonary bypass time between two groups was statistically significant ($p<0.05$).

Table-XI

Comparison of Pulmonary artery systolic pressure at 3 month after operation between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Pulmonary artery systolic pressure at 3 month after operation	Mean±SD 23.9±4.91	Mean±SD 27.9±5.16	0.02s

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was $p< 0.05$.
n = number of subjects; s = significant

Table-XII

Comparison of cardiopulmonary bypass time between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Cardio pulmonary bypass time (Minute)	Mean±SD 76.74±20.97	Mean±SD 93.16±27.18	0.04 s

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n = number of subjects; s = significant

Table-XIII compares mechanical ventilation time (Hours) between two study groups. Mean mechanical ventilation time (Hours) in group-1 was 10.75 ±7.27 and in group-2 was 15.9±8.21. It was observed that mean mechanical ventilation time (Hours) was significantly different between two groups (p< 0.05).

Table-XIII

Comparison of mechanical ventilation time (Hours) between two groups

Variable	Group 1 (n=20)	Group 2) (n=20)	P value
Mechanical ventilation time(Hours)	Mean±SD 10.75 ±7.27	Mean±SD 15.9±8.21	0.04 s

Data were expressed as Mean ± SD.
Statistical analysis were done by unpaired t-test. Level of significance was p< 0.05.
n = number of subjects; s = significant

Table- XIV demonstrates that there was no death in two groups.

Table-XIV

Comparison of death between two groups

Death	Group 1 (n=20)	Group 2) (n=20)	P value
Death up to discharge in post operative patients	0	0	
Death within 3 months after operation	0	0	

Discussion

The study was conducted in the department of cardiac surgery of Bangabandhu Sheikh Mujib Medical University and National Institute of Cardiovascular Diseases (*NICVD*) from February 2014 to February 2016 in left to right shunt atrial septal defect or ventricular septal defect or patent ductus arteriosus patients with moderate to severe pulmonary hypertension. Forty patients were selected for the study and were divided equally in group-1 and group-2. Twenty patients of group-1 received ambrisentan and another twenty patients of group-2 received sildenafil during preoperative and postoperative period. So far known that there was no available published data to compare between ambrisentan and sildenafil in pulmonary hyper-tension.

Sample size, duration of medication before surgery and variables for measuring surgical outcome of this study are consistent with the study conducted by Palma et al.[17] and Peiravian et al.[18] Moderate to severe pulmonary arterial hypertension patients were included in this study which was consistent with the study conducted by Palma et al.[17]

In Peiravian et al.[18], Palma et al.[17] and Midanya et al.[19] study reduction of mean pulmonary artery pressure occurred in patients receiving sildenafil. According to Galie et al.[20] and D'Alto et al.[21] mean pulmonary artery pressure significantly im-proved from baseline after 12 weeks in patients with pulmonary arterial hypertension receiving ambrisentan for 12 weeks. In this study pulmonary artery systolic pressure was reduced in both sildenafil and ambrisentan group. But more reduction of pul-monary artery systolic pressure was observed in ambrisentan group in comparison to sildenafil group at 7th post operative day, at 1 month after operation and at 3 month after operation in this study.

Palma et al.[17] found shortened cardiopulmonary bypass time and mechanical venti-lation time in a group receiving sildenafil preoperatively, peroperatively and post-operatively than the group receiving sildenafil from peroperatively. But in this study, cardiopulmonary bypass time and mechanical ventilation time was more short-ened in ambrisentan group than the sildenafil group.

Preoperatively cardiac catheterization was not performed in all cases. Colour Doppler echocardiography and direct intraoperative

measurements of pressure were the main-stays of estimation of pulmonary artery systolic pressure. Small sample size, lack of placebo group, purposively collection of samples, short observational duration are the limitations of the study.

For optimum dosing of ambrisentan and sildenafil in both paediatric and adult patients further study is needed. Large, multicentre, randomized, double-blind clinical trial with long-term follow-up is needed to validate the efficacy of ambrisentan and sildenafil in comparison with placebo or other vasodilators.

Conclusion:

Preoperative and postoperative therapy of ambrisentan had better surgical outcome than sildenafil in left to right shunt anomaly patients with moderate to severe pul-monary hypertension.

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