Outcome of Preoperative Administration of Oral Ambrisentan on Pulmonary Hypertension After Cardiac Surgery for VSD

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Introduction

Pulmonary artery hypertension (PAH) is a diverse group of diseases characterized by a progressive increase of pulmonary vascular resistance which leads to right ventricular failure and premature death if untreated. As the disease progresses and right ventricular after-load increases, the heart's ability to increase cardiac output with activity declines, resulting in exertional dyspnea, chest pain, or syncope. Eventually, progressive right heart dysfunction ensues, leading to right heart failure and death. The conventional definition of PAH used in clinical studies includes an mean pulmonary arterial pressure (mPAP) of greater than 25 mm of Hg at rest in the
setting of a normal pulmonary arterial wedge pressure of 15 mm of Hg or less with a pulmonary vascular resistance (PVR) greater than 3 Wood unit. PAH comprises a group of clinical and pathophysiological entities with similar features but a variety of underlying causes. Because the range of medical conditions and environmental exposures associated with PAH is wide, it is difficult to envision a unifying pathogenic mechanism. This classification system has 5 categories:

1. Pulmonary arterial hypertension (PAH). (Consists of three sub-groups)
   i) Idiopathic PAH (IPAH),
   ii) Familial PAH, and
   iii) PAH that is associated with specific conditions or risk factors.
2. Pulmonary hypertension related to left-heart disease.
3. Pulmonary hypertension related to lung disease or hypoxemia.
4. Chronic thrombotic or embolic pulmonary hypertension.
5. Miscellaneous.

In patients with systemic-to-pulmonary shunts, the type and size of the defect as well as the magnitude of the shunt are risk factors for the development of PAH. Shear stress due to increased pulmonary blood flow and/or increased Pulmonary artery pressure appears to play a major role in the development of pulmonary vascular disease (PVD) related to congenital heart disease (CHD). Pulmonary hypertension in paediatric patients with (VSD) remains one of the most important determinants of perioperative morbidity and mortality. Pulmonary hypertensive crisis is an important cause of morbidity and mortality in patients with PAH secondary to CHD who require cardiac surgery. Elevated pulmonary artery pressure in VSD is caused by pulmonary over circulation, pulmonary vasoconstriction and pulmonary vascular disease either alone or in combination. Endothelin-1, one of the most potent vasoconstrictors identified to date has been implicated in the pathobiology of PAH. Endothelin-1 expression, production, and concentration in plasma and lung tissue are elevated in PAH patients and inversely correlated with prognosis. Outcomes are significantly worse in patients with perioperative pulmonary hypertension (PH) and right ventricular (RV) failure prompting interest in the utility of newer therapies for this situation, including PAH-specific therapies. Persistent PAH after VSD surgery is with increased risk of mortality there was significant deference between the estimated survival between patient with and without PAH after VSD closure. In EURO Survey on adult congenital heart disease shows that PAH remains a risk factor in the long term clinical course of congenital heart septal defects. Patient mostly attending the specialized centers PAH was unexpectedly common and associated with worse functional status, more rapid clinical deterioration and enhance risk of death. Whether the prevalence of PAH will decline due to improved diagnostic and earlier treatment of CHD remains speculative. The diagnosis of (PH) relies on a high index of suspicion. In patients with symptoms or chest radiographic findings suggestive of PH, a detailed history and physical examination followed by early assessment with a transthoracic echocardiogram, ventilation-perfusion scanning, and chest computed tomography, pulmonary function testing, and nocturnal oxymetry screening can provide valuable information about etiology and severity. Cardiac catheterization should follow in patients who are symptomatic or who demonstrate moderate to severe PH by echocardiography and are candidates for treatment. Patients at risk for developing PH should undergo serial echocardiography and pulmonary function testing to assess for disease development and progression. Genetic testing is not currently recommended in the routine evaluation of patients with a diagnosis of primary PH.

Treatment Modalities:
Conventional Therapy:
- Supplemental Oxygen
- Diuretics
- Cardiac Glycosides
- Anticoagulation
Specific Treatments:
- Calcium-Channel Blockers
- Prostacyclin therapy
- Prostacyclin Analogues
- Endothelin-Receptor Antagonists
- Nitric Oxide
- Type 5 Phosphodiesterase Inhibitors
- Sildenafil
- Bosentan

Combination Therapy
It may be that the optimal approach to treating PAH is a combination of the above agents. This approach can be used for patients who do not respond to the initial monotherapy or who initially benefit but then deteriorate on a single agent. Multiple ongoing clinical trials are evaluating different combinations of agents. In a pilot study of acute administration of high doses of ambrisentan to patients with PH, pulmonary and systemic resistance decreased, suggesting that chronic doses might be necessary for a significant and selective effect.
In August 13, 2007, The US Food and Drug Administration (FDA) has approved an expanded indication for ambrisentan for the treatment of mildly symptomatic World Health Organization (WHO) functional class 2 to 4 (PAH).

The oral endothelin receptor antagonist Ambrisentan has been shown to improve the short and medium term course of adult pulmonary arterial hypertension.14

The routine preoperative oral administration of drugs aimed at reducing pulmonary hypertension and postoperative pulmonary hypertensive crisis is not still recommended in standard text book. Keeping that in mind we are trying to show in our study that preoperative administration of oral endothelin receptor antagonist ambrisentan is helpful in decreasing the pulmonary hypertension after surgical closure and post operative pulmonary hypertensive crisis.

Materials & Methods
The study was prospective, comparative study conducted at Department of Cardiac-surgery, National Institute of Cardiovascular Diseases (NICVD), Sher -E- Bangla Nagar, Dhaka from January 2014 to December 2014. All the patients fulfilling the inclusion and exclusion criteria undergoing surgical closure of VSD with PAH (moderate to severe) at NICVD during the given period were the study population. The participants were explained the purpose of the study and also the importance of such study. The study was conducted with signed informed consent of all the participants with the right to withdraw himself/herself from the study at any time during the study period. Interest of study was given highest priority and confidentiality was be maintained with safe guard of the right and health of the participants. Sampling technique was purposive and convenient. Samples were selected according to inclusion and exclusion criteria. Inclusion Criteria was patients with VSD with moderate and severe PH. Exclusion Criteria were age less than 2 and more than 15 years, associated other congenital anomaly, associated valve disease, PVR >8 Wood's unit/meter square body surface area, pulmonary vascular resistance without reversibility, VSD associated with primary PH. Variables were:

Demographic variables: age and sex. Pre-operative variables (Before use of Ambrisentan): Echocardiogram PASP (mm of Hg) and cardiac catheterization PA pressure (mm of Hg),Qp/Qs and PVR in woods unit. Per-operative variables: PA pressure(Measured directly from PA before correction and after weaning from CPB), ECCT in minutes, XCT in minutes. Post-operative variables: Echocardiogram PASP (mm of Hg), mechanical ventilation time in hours, ICU stay in days. Patients admitted in the cardiac surgery department, NICVD, fulfilling the inclusion and exclusion criteria were included in this study.

A total of 54 patients were selected after confirmation of diagnosis by echocardiogram detecting presence of VSD and PH. Patients were divided into two groups. The Group-A consists of 27 patients who received ambrisentan two weeks before surgery. The other group that is Group-B did not receive ambrisentan and this group was considered as control. The dose of the drug ambrisentan was adjusted according the body weight of the patient. Patient weighing < 20 kg got 2.5 mg of ambrisentan in two divided doses per day and patient weighing >20 kg got 5 mg of ambrisentan in two divided doses per day for at least two weeks before surgery.

Surgical technique
All patients were operated as per this local institutional protocol under CPB and by median sternotomy. Peroperatively PA pressure was recorded before establishment of CPB, just after surgical closure of VSD with PTFE patch and after weaning from CPB with stable haemodynamics directly from PA. Peroperative XCT and ECC were also recorded.

ICU management:
All patients were taken into intensive care unit (ICU) after completion of operation and after extubation ambrisentan was continued. If prolong ventilation requires, ambrisentan was administered through ryle's tube. In case of development of RV failure (manifested by raised CVP, hypotension, reduced SPO2) pulmonary vasodilators were used in both group of patients. Duration of ICU stay, ventilator support, development of RV failure, duration of hospital stay were recorded and compared between two groups. Data were collected, recorded and interpretation was done by using SPSS version (Version-16).

Results
Table I: Comparison of age distribution between Group A and Group B.

| Age (year) | Group A (n=27) | Group B (n=27) | p-value |
|-----------|----------------|----------------|---------|
| 3 - 5 | 9 (33%) | 8 (30%) | 0.324 |
| 6 - 8 | 8 (30%) | 8 (30%) | 0.314 |
| 8 - 9 | 10 (37%) | 11 (40%) | 0.401 |
| Total | 27 (100.0%) | 27 (100.0%) | 0.312 |
| Mean±SD | 5.30 ± 1.787 | 5.87 ± 1.97 | 0.360 |

Table I: shows the distribution of patient of various age groups in percentage and also the mean age. There is no significant difference in distribution of various ages of patient among two groups.
Figure 1: Comparison of sex distribution between Groups.

Figure-1: shows that females were predominant in Group-A (55.5%) and males were in Group-B (52%). There is no significant difference between the groups considering sex distribution. (P value=.749).

Table II. Comparison of preoperative variables between groups

| Preoperative findings                        | Group A mean±SD | Group B mean±SD | P value |
|----------------------------------------------|-----------------|-----------------|---------|
| PASP (mm of Hg) on echocardiogram            | 70.96 ± 10.80   | 71.40 ± 10.89   | 0.895   |
| PASP on cardiac cath.                        | 71.33 ± 10.69   | 71.29 ± 11.18   | 0.629   |
| Qp:QS in Cardiac cath.                      | 2.62 ± 3.83     | 1.90 ± 0.13     | 0.62    |
| PVR in cardiac cath                          | 4.66 ± 0.83     | 4.55 ± 0.80     | 0.94    |

Table II shows preoperative variables data between the groups showing PASP on echocardiogram, PASP on cardiac cath, Qp/Qs and PVR.

Table III. Comparison of Peroperative PASP between groups

| Per-operative findings                        | Group A mean±SD | Group B mean±SD | P value |
|----------------------------------------------|-----------------|-----------------|---------|
| PA pressure (before establishment of CPB)    | 59.55 ± 11.16   | 71.92 ± 10.62   | 0.002   |
| PA pressure (just after closure of VSD on CPB)| 45.49 ± 9.46   | 66.34 ± 10.22   | 0.001   |
| PA pressure (after weaning from CPB)         | 40.49 ± 10.33   | 62.14 ± 9.46    | 0.001   |

Table III showing the peroperative comparison of PASP before establishment of CPB, just after closure of VSD and after weaning from CPB between the two groups. Peroperatively PA pressure was recorded before CPB establishment, after VSD closure and after weaning from CPB with stable haemodynamics directly from PA. There were significant differences regarding reduction of PASP between the groups.

Table IV: Comparison of per-operative variables between groups.

| Peroperative findings      | Group A mean±SD | Group B mean±SD | P value |
|----------------------------|-----------------|-----------------|---------|
| Aortic Xclamp time (min)   | 52.18 ± 2.03    | 53.25 ± 1.48    | 0.56    |
| ECCT (min)                 | 82.33 ± 4.42    | 87.22 ± 5.89    | 0.48    |

Table-IV: showing the per-operative aortic X-clamp time and extracorporeal circulation time (ECCT) and that were compared between the two groups. There were no significant differences regarding cross clamp time and extracorporeal circulation time between the groups.

Table V: Comparison of postoperative PASP outcome between groups

| Postoperative outcome       | Group A (n = 27) | Group B (n = 27) | p value |
|-----------------------------|-----------------|-----------------|---------|
| Postoperative PASP at 7th POD| 33.55±1.23      | 41.70±5.60      | .001    |
| Postoperative PASP at 1 month| 30.55±2.26      | 39.11±3.28      | .001    |

Table-V: showing the post-operative PASP in two groups and the reduction is significantly higher in ambrisentan group. PASP was measured postoperatively and was found significantly lower (0.001) in ambrisentan group than control group.

Table VI. Comparison of Postoperative ventilation time and ICU stay

| Per-operative findings      | Group A mean±SD | Group B mean±SD | p value |
|-----------------------------|-----------------|-----------------|---------|
| Ventilation time (hours)    | 5.96 ± 0.758    | 11.14 ± 1.32    | 0.013   |
| ICU stay (days)             | 3.66 ± 0.78     | 6.11 ± 0.50     | 0.001   |

Table-VI: showing the postoperative comparison of ventilation time and ICU stay and that were compared between the two groups. There were significant differences regarding ventilation time and ICU stay between the groups.

Discussion

Pulmonary hypertension is a common situation encountered in common cardiac surgical procedure. In this study we concentrated pulmonary arterial hypertension (PAH) excluding other four groups of diseases responsible for pulmonary...
hypertension. Even in that particular group of PAH we focused on congenital heart disease ventricular septal defect (VSD) with left to right shunt who presented with raised pulmonary artery systolic pressure (PASP). All patients underwent right heart catheterization to confirm the pulmonary vascular resistance (PVR), to measure the Qp/Qs ratio and for the purpose of reversibility testing. After consideration of selection criteria patients were divided into two groups one group that is treated with preoperative oral ambrisentan and the other group without ambrisentan. In this study age of patients varied from 3 to 9 years and the mean age was 5.30±1.787 years in ambrisentan group and 5.87±1.97 years in control group with no statistical significant difference (p=0.360) between the mean ages (Table I). Regarding sex distribution, in our study 9 out of 15 (60%) patients were male in ambrisentan group and 8 out of 15 (53.33%) patients were male in control group with no statistically significant variation (p-0.713) between the groups (Figure I). Considering the preoperative variables like PASP on echocardiogram and on cardiac catheterization, Qp/Qs ratio and PVR were compared between the two groups and there was no significant difference between two groups. PASP was measured by echocardiogram was 70.96 ±10.80 mm of Hg in the ambrisentan group and was 71.40 ±10.89 mm of Hg in the control group with a p value of 0.895 (Table II).

PVR was measured in all patients of both the groups and their mean was 4.66 ±0.83 in the ambrisentan group and was 4.55 ±0.80 in the control group. There was no significant difference of between the groups (Table II). PASP was measured peroperatively before establishment of CPB, immediately after VSD closure and after weaning from CPB which were 59.55±11.16 mm of Hg, 45.49±9.46 mm of Hg and 40.49 ±10.33 mm of Hg respectively in the ambrisentan group (Group-A) and was 71.92 ±10.62 mm of Hg, 66.34±10.22 mm of Hg and 62.14 ±9.46 mm of Hg respectively in the control group (Group-B) with a p value of 0.002, 0.001 and 0.001 respectively (Table III). There was significant reduction of PASP both before CPB establishment, just after VSD closure and after weaning from CPB in patients who were treated with preoperative oral ambrisentan. Operative variables also included cross clamp time (XCT), extra corporeal circulation time (ECCT). In the ambrisentan group XCT was 52.18 ± 2.03 minutes and in the control group it was 53.25 ± 1.48. ECCT was 82.33 ± 4.42 in ambrisentan group and 87.22 ± 5.89 in control group (Table IV). Considering PASP on echocardiogram at 7th post-operative day was 33.55 ± 1.23 in ambrisentan group and 41.70 ± 5.60 in control group. At one month PASP on echocardiogram was 30.55 ±2.26 in ambrisentan group and 39.11 ±3.28 in control group. There is significant difference with p value of 0.001 and PA pressure is significantly reduced following ambrisentan treatment (Table V). Mechanical ventilation time was significantly (0.13) lower (5.96 ±.758 hours) in ambrisentam group than in control group (11.14 ±1.32 hours). ICU stay was 3.66 ±0.78 days in ambrisentan group and was 6.11 ± 0.50 days in control group (Table VI). No patient died during the study period of both the study groups. We used to continue oral ambrisentan for at least two months postoperatively for smooth recovery of the disease. For this reason we could not asses like other studies the rebound pulmonary hypertension following discontinuation of the drug.

Conclusion
In conclusion, it can be stated that there is significant reduction in pulmonary hypertension both before and after surgical closure of VSD with the use oral ambrisentan preoperatively. So ambrisentan can be considered as an attractive and effective oral therapy for moderate to severe pulmonary hypertension. It is safe and easy to administer and inexpensive. We conclude that oral ambrisentan should be advised preoperatively for every patient with VSD with moderate to severe pulmonary hypertension.

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References
1. Simonneau, G, Galiè, N, Rubin, L.J. "Clinical classification of pulmonary hypertension." Journal of American College of Cardiology 2004; 43 (1): 5-12.
2. Barst, D.B., Abman, S.H., Ahearn, G.S., McCrory, D.C., Simonneau, G., Mc Laughlin, V.V. "Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines." Chest 1996; 126 (1): 35-62.
3. Mc Laughlin, V.V., Gentnher, D.E., Panella, M.M., Rich, S. "Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. New England Journal of Medicine 1998; 338 (5): 273-277.
4. Khalili, Y. "Pulmonary Arterial Hypertension." The Iranian Journal of Cardiac Surgery", 2008; 2(1): 4-8.

5. Kaplan, B., Butler, H., Krishbom, P., Kanter, K., Mcconnell, M. "Closure of symptomatic ventricular septal defects: How early is too early?" Pediatric Cardiology, 2002; 29, 36-39.

6. Midany, A., Sunnegårdh, J., and Berggren, H. Preoperative evaluation and surgery in isolated ventricular septal defects: a 21 year perspective." Heart 2013; 83:198-204.

7. Bruner K. L., Ridout, D. A., Hoskote A., Verhulst, L., Ricci, M., and Bul, C. "Delayed diagnosis of congenital heart disease worsens preoperative condition and outcome of surgery in neonates." Heart 2014; 92: 1298-1302.

8. Berger, M.R., Zisman, L.S., Lowes, B.D., Abraham, W.T., Badesch, D.B., and Groves, B.M. "The pressure-overloaded right ventricle in pulmonary hypertension." Chest 2002; 114 (1): 101-106.

9. Yanagiswa, H., Yoshitoshi, M., and Miyamoto, A.T. "Ventricular septal defect: selection of patient and timing of surgery." American Heart Journal 1988; 40-50.

5. Kaplan, B., Butler, H., Krishbom, P., Kanter, K., and Mcconnell, M. "Closure of symptomatic ventricular septal defects: How early is too early?" Pediatric Cardiology, 2002; 29: 36-39.

10. Malouf, K., Ilhkem, K., Buckberg, G.D., Sherman M.P. and Ignore, L.J."Pulmonary vasoconstriction due to impaired nitric oxide production after cardiopulmonary bypass." Annals of Thoracic Surgery 2002; 61: 1775-1780.

11. Engelfriet, P.M., Duffels, M.G., Moller, T., Boersma, E., Tijssen, J.G., and Mulder, B.J. "Pulmonary arterial hypertension in adults born with a heart septal defect : the Euro Heart Survey on adult congenital heart disease." Heart 2007; 93: 682-687.

12. Budev, B., Gatzoulis, M.A., and Jennings, A. "Pulmonary arterial hypertension in adults with congenital heart disease." Cardiology, 2003; 58: 465-469.

13. Richard, V. M., Carl, J. L., and Andres, R."Clinical correlates and reference intervals for pulmonary artery systolic pressure among echo-cardiographically normal subjects." Circulation, 2001;104: 2797-2802.

14. Beghetti, M., and Tissot, C. "Pulmonary Hypertension in Congenital Shunts, American College of Cardiology 2008; 63(10):1179-1193.