

## Original Article

# Sildenafil in Perioperative Management of Congenital Shunt Anomaly Patients with Pulmonary Hypertension

ASM Iftekher Hossain<sup>1</sup>, Nazmul Hosain<sup>1</sup>, Syed Monirul Islam<sup>2</sup>, AYM Shahidullah<sup>3</sup>, Zahidur Rahman<sup>4</sup>, Mamunur Rahhman<sup>5</sup>, Md Abul Kashem<sup>6</sup>

<sup>1</sup>Dept. of Cardiac Surgery, Chittagong Medical College, Chittagong, <sup>2</sup>Dept of Cardiac Surgery, Sir Salimullah Medical College, Dhaka, <sup>3</sup>Fortis Escorts Heart Institute, Khulna, <sup>4</sup>Sadar hospital, Jhenidah, Jessore, <sup>5</sup>Dept of Cardiac Anesthesia, Chittagong Medical College. <sup>6</sup>Dept. of Cardiac Surgery, NICVD, Dhaka

## Abstract:

### Key Words :

Congenital cardiac lesion, Shunt anomaly, Sildenafil, Pulmonary hypertension.

**Background:** Congenital heart diseases (CHD) are associated with an increased risk for the development of pulmonary vascular disease. Severe and irreversible pulmonary hypertension may then ensue and, eventually, leads to reversal of the shunt. Oral sildenafil is used for preoperative and postoperative treatment of pulmonary hypertension.

**Methods:** A total of 30 patients, who underwent surgical closure of congenital anomaly i.e. ASD and VSD with High Pulmonary Pressure were included in the study. Patients were initially selected by echocardiogram showing pulmonary arterial systolic pressure (PASP) more than 40 mm of Hg. The Group A (sildenafil group) consisted of 15 patients and had received sildenafil during and after operation was given to these patients initially through nasogastric tube and later via the oral route 6 hourly for 44 hours.

**Results:** Reduction in the PA pressure in sildenafil group was found statistically significant ( $p=0.044$ ). ICU stay and total hospital stay were shorter in the intervention group than the control but not statistically significant possibly due to smaller sample size.

**Conclusion:** We conclude that oral sildenafil treatment is a safe, simple and effective alternate for persistent pulmonary hypertension early after congenital cardiac surgery.

(*Cardiovasc. j.* 2019; 12(1): 9-12)

## Introduction:

Congenital heart disease (CHD) is the commonest of all congenital lesions and is the most common type of heart disease among children.<sup>1</sup> Early studies of CHD found the incidences of about 4 to 5 per 1,000 live births, but this figure has been rising steadily until recently when incidences of 12 to 14 per 1,000 live births, or higher, have been reported in some literature.<sup>2</sup> World Health Organization (WHO) reports, among all cardiovascular disease, the incidence of congenital heart disease in Bangladesh is around 6%. Different forms of CHD are associated with an increased risk for the development of pulmonary vascular disease (PVD).

Severe and irreversible pulmonary hypertension (PHTN) may then ensue and, eventually, leads to reversal of the shunt.<sup>3</sup>

Oral sildenafil is used for preoperative and postoperative treatment of pulmonary hypertension. Sildenafil citrate, a Phosphodiesterase type 5 (PDE 5) inhibitor, developed for the treatment of erectile dysfunction has been used as an alternative to traditional therapies. It has been used to treat various types of PH.<sup>4</sup> It is reported that sildenafil has beneficial hemodynamic effects when administered by nasogastric tube in patients undergoing cardiac surgery who develop intraoperative PHTN.<sup>5</sup> For more persistent PHTN

**Address of Correspondence:** Dr. ASM Iftekher Hossain, Dept. of Cardiac Surgery, Chittagong Medical College, Chittagong, Bangladesh. E-mail: [dr.iftkher@gmail.com](mailto:dr.iftkher@gmail.com)

© 2018 authors; licensed and published by International Society of Cardiovascular Ultrasound, Bangladesh Chapter and Bangladesh Society of Geriatric Cardiology. This is an Open Access article distributed under the terms of the CC BY NC 4.0 (<https://creativecommons.org/licenses/by-nc/4.0>).

following cardiac surgery, oral pulmonary vasodilators may be considered. A case series suggested that oral sildenafil may be helpful in weaning patients from intravenous or inhaled pulmonary vasodilators for PHTN following cardiac surgery.<sup>6</sup>

Pathologic processes behind the complex vascular changes associated with PHTN include vasoconstrictor-vasodilator imbalance, thrombosis, misguided angiogenesis, and inflammation. Since the introduction of the selective PDE5 inhibitor sildenafil citrate, there has been growing evidence of its efficacy in treatment of both primary and secondary PHTN. Its availability in oral, inhaled, and intravenous forms, its relative high degree of pulmonary selectivity, and its longer half-life than other pulmonary vasodilators are distinguishing features that make sildenafil a potentially useful drug for managing perioperative PHTN.<sup>7</sup> We therefore had examined the effect of oral sildenafil administered during and immediately after surgery on hemodynamics in patients with concomitant PHTN undergoing congenital heart surgery in a prospective trial.

### Methods:

This prospective clinical study was carried out in the Department of Cardiac Surgery, National Institute of Cardiovascular Diseases (NICVD), Dhaka from January 2009 to December 2010. Patients of basic isolated shunt anomaly type congenital heart disease with PHTN (pulmonary arterial systolic pressure >40mm of Hg) were included. Exclusion criteria were PASP more than 90 mm of Hg, failure to show significant positive result at reversibility testing, presence of chronic obstructive pulmonary disease, concomitant hepatic or renal disease, complex congenital heart disease etc. Total of 30 patients were included in this study and the patients were divided into two groups- Group A (sildenafil group): Patients receiving sildenafil; Group B (control group): Patients not receiving sildenafil. Informed written consent was taken from the patients or their guardians. The study protocol was approved by the ethical committee of NICVD.

Patients were initially selected by echocardiogram showing pulmonary arterial systolic pressure (PASP) more than 40 mm of Hg. The Group A

(sildenafil group) consisted of 15 patients and had received sildenafil during and after operation. Sildenafil was given to these patients through nasogastric tube or via the oral route every 6 hours with a dose of  $0.5 \text{ mg} \cdot \text{kg}^{-1}$  of body weight. It was initiated at the time of induction of anesthesia and continued in the same dose for 48 hours after surgery. The dose of sildenafil then adjusted according to response of the patient. The Group B (control group) consisted of 15 patients did not receive sildenafil. Conventional treatment practised at NICVD was given to all patients irrespective of mentioned grouping based on sildenafil use.

Closure of the atrial or ventricular shunt was done in both groups according to conventional procedure practiced at NICVD using cardiopulmonary bypass. After closure of the congenital cardiac shunts and withdrawal from the cardiopulmonary bypass pulmonary artery pressure was measured directly. All patients were taken into intensive care unit (ICU) after operation and standard NICVD protocol was applied. Patients were monitored carefully in the immediate postoperative period to diagnose any events of pulmonary hypertensive crisis so that it can be managed without delay. Postoperative adverse effects of drug used like flushing, headache and diarrhea were recorded.

Echocardiogram was done to all the patients on 1<sup>st</sup> and 2<sup>nd</sup> postoperative day to measure the PASP and their mean was calculated for comparison with the PASP of preoperative echocardiogram. Data were collected through interview, investigation & hospital records and were put in a pre-designed questionnaire and a computerized data file was constructed. All data were analyzed by using computer based Statistical Package for Social Sciences (SPSS, version 11).  $p$  value <0.05 was considered significant.

### Results:

Mean age in the sildenafil group was  $16.40 \pm 7.12$  years and that of control group was  $16.87 \pm 7.82$  years with no significant difference between the groups with respect to age ( $p = 0.866$ ). Males were predominant in both groups (60% in Group-A 53.33% in Group-B) with no significant difference between the groups with respect to gender ( $p = 0.713$ ).

**Table-I**  
*Comparison of postoperative outcome between groups (N=30).*

Postoperative outcome	Group		p value
	Sildenafil Group (n = 15)	Control Group (n = 15)	
PA Pressure (mm of Hg) mean pressure	33.60 ± 5.34	38.13 ± 6.39	0.044
Aortic pressure (mm of Hg)	100.93 ± 6.72	96.47 ± 4.26	0.038
PA/Ao ratio	0.333 ± 0.049	0.398 ± 0.074	0.008
PASP on echocardiogram	30.73 ± 3.58	35.53 ± 6.32	0.016
Ventilation time (hrs)	7.13 ± 1.767	8.93 ± 2.57	0.033
ICU stay (hours)	62.67 ± 9.45	70.13 ± 13.58	0.092
Hospital stay (days)	8.87 ± 1.12	9.13 ± 1.35	0.167

Data were analyzed using Student's T Test and were presented as mean ± SD.

The pulmonary pressure (PA), Aortic pressure (Ao), PA/Ao ratio, PVR and mean partial pressure of oxygen (SpO<sub>2</sub>) were compared between the two groups. Preoperative PASP was also measured with echocardiogram and compared between the groups. There was no significant (p value > 0.05) difference between the groups regarding these preoperative variables. There was no significant difference regarding cross clamp time between the groups. Extracorporeal circulation time (ECCT) was found little higher in the control group though it was not statistically significant.

The postoperative mean PA pressure and PA/Ao ratio reduced in both the groups but the reduction is significantly higher in sildenafil group (Table 1). Mechanical ventilation time was found significantly higher in control group. PASP was measured postoperatively and was found significantly lower (< 0.05) in sildenafil group than control group. ICU stay and total hospital stay were higher in the control group though that was not statistically significant (> 0.05).

Headache, diarrhea, and flushing were observed among a few patients of sildenafil group. There was no significant difference regarding complication among the groups (p > 0.05). One patient was expired in the control group due to low output syndrome from right heart failure. That was not significant statistically.

#### Discussion:

Pulmonary hypertension is not an uncommon situation encountered in common cardiac surgical procedures. Pulmonary arterial mean pressure was

33.60 ± 5.34 mm of Hg in the sildenafil group and was 38.13 ± 6.39 mm of Hg in the control group. Reduction in the PA pressure in sildenafil group was found statistically significant (p = 0.044). These findings correspond with the findings of Peiravian et al.<sup>8</sup> {from 76.8 ± 17.4 to 28.6 ± 7.8 mm of Hg (p < 0.001)} and that of Nemoto et al.<sup>9</sup> Mechanical ventilation time was significantly (p = 0.033) lower (7.13 ± 1.77 hour) in sildenafil group than in the control group (8.93 ± 2.57 hour) and this finding corresponds with the study of Peiravian et al.<sup>8</sup> and that of Nemoto et al.<sup>9</sup> ICU stay was 62.67 ± 9.45 hours in sildenafil group and was 70.13 ± 13.58 hours in the control group. Though ICU stay was reduced in the intervention group than the control and it was not statistically significant possibly due to smaller sample size. Peiravian et al.<sup>8</sup> also reported reduction in the ICU stay. Total hospital stay was 8.87 ± 1.12 days in the sildenafil group and was 9.13 ± 1.35 days in the control group and this (p = 0.562) also have got the similarity with the study of Peiravian et al.<sup>8</sup> Findings in both the studies were insignificant. 3 out of 15 patients developed headache, and 2 patients developed flushing of face, transient erection of penis and diarrhoea in the sildenafil group. All these effects were relieved in a few days. We used to continue oral sildenafil for at least two months postoperatively for smooth recovery of the disease. For this reason, we could not assess, like other studies, the rebound pulmonary hypertension following discontinuation of the drug. A patient was expired in the control group possibly due to low output syndrome from right heart failure.

All acceptable medications used for the control of postoperative pulmonary hypertension in standard and well-equipped heart centers are expensive and difficult to introduce. For example, inhaled NO needs closed ventilation circuit for introduction and not available in our country. Phenoxybenzamine, though used in our ICU it is expensive and still not approved by US FDA.

#### **Conclusion:**

Sildenafil can be considered as an attractive and effective oral therapy for postoperative pulmonary hypertension. It is safe, easy to administer, and inexpensive. Careful long-term follow-up and conduction of a double-blind clinical trial are required to examine the effects of sildenafil further.

---

#### **Conflict of Interest - None.**

---

#### **References:**

1. Schoen, F.J., 1999. The Heart. In: Cortan RS, Kumar V, Robins SL. Eds. *Robins pathological basis of disease*. 6<sup>th</sup> edn. Philadelphia: Elsevier Saunders, 1999:543-600.
2. Hoffman JIE, Kaplan S. The Incidence of Congenital Heart Disease. *J Am Coll Cardiol* 2002; 39: 1890-1900.
3. Thomson, JDR. Congenital heart disease. In: Julian DG, Cowan JC, Mclenachan JM. Eds. *Cardiology*. 8<sup>th</sup> edn. USA: Elsevier, 2005: 274-275.
4. Reffelmann T, Kloner RA. Therapeutic potential of phosphodiesterase 5 inhibition for cardiovascular disease. *Circulation* 2003; 108: 239-244.
5. Madden BP, Sheth A, Ho TB. Potential role for sildenafil in the management of perioperative pulmonary hypertension and right ventricular dysfunction after cardiac surgery. *Br J Anaesth* 2004; 93: 155-156.
6. Trachte AL, Lobato EB, Urdaneta F, Hess PJ, Klodell CT, Martin TD, et al. Oral Sildenafil Reduces Pulmonary Hypertension After Cardiac Surgery. *Ann Thorac Surg* 2005; 79: 194-197.
7. Jackson M, Walsh KP, Peart I, Arnold R. Epidemiology of congenital heart disease in Merseyside-1979 to 1988. *Cardiol Young* 1996; 6: 272-280.
8. Peiravian F, Amirghofran AA, Borzouee M, Ajami GH, Sabri MR, Kolaee S. Oral Sildenafil to Control Pulmonary Hypertension after Congenital Heart Surgery. *Asian Cardiovasc Thorac Ann* 2007; 15: 113-117.
9. Nemoto S, Sasaki T, Ozawa H, Katsumata T, Kishi K, Okumura K. Oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in children. *Eur J Cardiothorac Surg* 2010; 38:71-77.