Original Article

Perioperative sildenafil therapy for children with ventricular septal defects and associated pulmonary hypertension undergoing corrective surgery: A randomised clinical trial

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ABSTRACT

Background and Aims: Sildenafil is known to reduce pulmonary artery pressure but its role in the perioperative period has not been well studied. We aimed to evaluate the efficacy of sildenafil in controlling post-operative pulmonary hypertension in children with pulmonary hypertension undergoing surgeries for correction of ventricular septal defect. **Methods:** The patients were divided randomly into two groups of thirty each. Group 1 (placebo) received pre-operative placebo and post-operative sildenafil (0.5mg/kg every 6 hrs) while Group 2 (sildenafil) received pre- and post-operative sildenafil (0.5mg/kg every 6 hrs) **Results:** In the Group 1, systolic pulmonary artery pressure reduced from 81.63 (±12.1) mmHg preoperatively to 79.26 (±11.29) mmHg pre-cardiopulmonary bypass (CPB) and 56.76 (±11) mmHg (with 10 minutes post-CPB), whereas in Group 2, it reduced from 83.3 (±12.1) before surgery to 68.9 (±11.3) mmHg pre-CPB and after CPB, to 42.2 (±7.6) mmHg (P = 0.001). The mean pulmonary artery pressure decreased from 60.63 (±10.5) mmHg to 42.13 (±8.3) mmHg in the Group 1 whereas it reduced from 54.36 (±10) mmHg to 31.36 (±6.5) mmHg in Group 2 (P = 0.001). The reductions in pulmonary artery/aortic ratio and Intensive Care Unit stay were statistically significant No adverse effects were recorded. **Conclusion:** The use of perioperative sildenafil has a statistically significant reduction in the mean pulmonary artery pressure without any adverse effects.

Key words: Pulmonary artery pressure, sildenafil, ventricular septal defect

INTRODUCTION

Pulmonary artery hypertension (PAH) associated with congenital heart defects in children is a major cause of post-operative morbidity and mortality.[1] Sildenafil has been used to treat PAH in adults and children.[2] Sildenafil is a selective phosphodiesterase-5 inhibitor which increases the bioavailability of cyclic guanosine monophosphate and thus supports endogenous vasodilatation.[3] Sildenafil has useful effects in PAH, particularly in chronic therapy and in attenuating rebound effects after inhalation nitric oxide (iNO) is discontinued.

Endothelin-receptor blockers, continuous iNO and aerosolized prostacyclin and analogues are newer emerging therapies.[4] The use of these is limited by cost, systemic side effects, complications of prolonged intravenous (IV) access and rebound pulmonary hypertension.[5]

Recent studies using monotherapy of sildenafil have shown that it has a significant clinical benefit. Sildenafil is well-tolerated drug and is readily available

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as an oral preparation. This is helpful to the patients of PAH as their symptoms do not warranty continuous IV infusions.[6]

In our institution, sildenafil is routinely used postoperatively; therefore, we designed this study to evaluate the efficacy of sildenafil in controlling post-operative pulmonary hypertension in children undergoing cardiac surgeries for ventricular septal defect (VSD) correction.

METHODS

After approval by the hospital ethical committee and parental consent, we recruited 60 paediatric patients with VSD with PAH due for corrective surgery from October 2012 to March 2014 in this randomized control trial. The presence of VSD and PAH was confirmed by a two-dimensional echocardiography, and the value of pulmonary artery pressure (PAP) was assessed by cardiac catheterization. Patients included in the study were those who had systolic PAP >35 mmHg or mean PAP >25 mmHg with large VSD and low Qp:Qs (pulmonary blood flow:systemic blood flow) along with high pulmonary vascular resistance. Attempts were made to determine the reactivity of pulmonary vasculature by administering 100% oxygen in patients with mean PAP >35 mmHg. Patients with associated congenital heart defects other than VSD and any genetic syndrome were excluded from the study.

Patients were randomly allocated into two groups: Group 1 (placebo) received pre-operative placebo and post-operative sildenafil while Group 2 (sildenafil group) was administered pre- and post-operative sildenafil. The nurses administering the drugs were blinded to the intervention for either group. Sildenafil (0.5 mg/kg) or equivalent volume placebo was administered 6 hourly orally or by nasogastric tube for 1 week before surgery. Postoperatively, sildenafil was administered at 0.5 mg/kg 6 h and increased to 1 mg/kg 6 hourly over the next 2 days and further continued till 15 days during which the patients were followed for complications after the surgery. Drug was prepared by one of the coinvestigators. In the post-operative period, sildenafil was administered intravenously (0.5mg/kg every 6 hrs) for the first 24 h and then switched to orogastric route through the Ryles tube and this was common for both the groups. Measurements such as systolic, diastolic and mean PAP, systemic arterial pressures (SAPs) (systolic/diastolic/mean) and oxygen saturation were recorded during intraoperative period, and PAP/SAP ratios were calculated before and after the correction of the VSD (within 10 min of the correction). Pressure monitoring device was set-up similar to the arterial line (invasive blood pressure) setup device, and a sterile pressure monitoring line was handed over to the surgeon who then inserted a needle in the pulmonary artery and attached it to the pressure monitoring line. The Pulmonary Artery pressures were measured pre- and post-repair of Ventricular Septal Defect (Primary Outcome being the mean PAP). The technicians noting down the pressures and nurses in the ICU were blinded to the intervention. Demographic data, type of congenital heart disease (CHD), duration of cardiopulmonary bypass (CPB), aortic cross-clamping, duration of surgery, duration of ventilation, Intensive Care Unit (ICU) stay, sepsis and mortality (30-day mortality) were also noted in the two groups (Secondary Outcomes). Pulmonary hypertensive crisis was diagnosed when any patient experiencing pulse oximetry desaturation (<70%), hypotension (<60/30 mmHg), tachycardia followed by bradycardia (<30/min) and ST-segment changes on ECG in the post-operative period, in the absence of left ventricular dysfunction by echocardiography:[7]

Institutional anaesthetic protocols along with all necessary monitoring were used. The surgery was conducted on CPB using moderate hypothermia (core body temperature of 32°C). Cardioplegic arrest was achieved with St. Thomas cardioplegic solution. After completion of surgery, patients were weaned off CPB, with inotropic and vasoactive drug support, so as to maintain a mean arterial pressure above 50 mmHg. The patients were shifted to the cardiac ICU with endotracheal tube *in situ* and electively ventilated. The trachea was extubated when the patient met the extubation criteria.

All statistical analysis was done using SPSS 17.0(IBM- USA). For comparing non-parametric categorical data between groups, Chi-square test was used. To compare means between two groups, unpaired *t*-test was used. $P < 0.05$ was taken to be statistically significant.

RESULTS

There was no difference in the demographic variables such as age, gender, height and weight in the two groups as illustrated in Table 1. The presenting

symptoms were also quite similar in the two groups as shown in Table 2.

There was no significant difference in CPB time or in aortic cross-clamp time between the two groups as shown in Table 3.

In the Group 1, the pre-operative systolic pulmonary artery pressure (1 week before surgery) was 83.3 (±12.1) mmHg whereas, in the Group 2, it was 81.63 (±12.1) mmHg.

It was found that the pre-CPB PAP difference was statistically significant between the two groups., The difference in the pre-CPB mean PAP between the two groups was statistically significant ($P = 0.021$). The pre-CPB systemic intra-arterial pressure difference between the two groups was not significant for systolic and diastolic values, but it was statistically significant for the mean arterial pressure values ($P = 0.045$).

The above-mentioned pre-operative values in both the groups have been demonstrated in Table 4.

The post-CPB PAP difference was highly significant between the two groups ($P = 0.001$). Pulmonary artery/aortic pressure ratio between both the groups was also statistically significant ($P = 0.001$).

No sepsis was reported in any of the patients in either of the two groups Although there was no difference in the mortality and morbidity between the two groups, ICU stay was significantly shorter in the sildenafil group (78.46 h) as compared with the placebo group (98.4 h) ($P = 0.001$). The above-mentioned post-operative variables between the two groups have been illustrated in Table 5.

A marked effect of pre- and post-operative sildenafil administration was observed on mean PAP (mPAP) as reflected by the progressive significant decrease of the mPAP from baseline to immediate pre-CPB to immediate post-CPB in both the groups.

Incidences of post-operative pulmonary hypertensive crisis were present in both the groups. In Group 1, only one patient had three episodes of pulmonary artery hypertensive crisis whereas, in Group 2, two patients had two episodes each of pulmonary artery hypertensive crisis.

DISCUSSION

We found that that there is a significant reduction in pulmonary artery pressures in the group consuming sildenafil in the pre-operative period. The post-CPB pulmonary artery pressure difference was highly significant between the two groups ($P < 0.001$) which means that the use of sildenafil in patients in the pre-operative period along with post-operative period reduces pulmonary artery pressures much more than in patients where it is used in post-operative period only. Few studies have proved the beneficial effects of sildenafil in reducing PAH.[2,8,9]

One of the main challenges to deal with in paediatric cardiac surgery is pulmonary arterial hypertension secondary to congenital heart disease. The conventional management requires the need of special delivery systems for the administration of iNO, the need to maintain continuous IV drug infusions and inadequate response to conventional therapy, is costly

Table 1: Demographic distribution - age, gender, height and weight

Variable	Mean±SD		Mean difference	*t*	*P*
	Group 1 (*n*=30)	Group 2 (*n*=30)			
Age (months)	15.83±13.06	14.53±12.62	1.30	0.392	0.696
Gender					
Female	15 (50%)	17 (56.7%)	0.605 (*P* value)		
Male	15 (50%)	13 (43.3%)			
Height (cm)	71.20±10.10	72.70±10.19	1.50	0.572	0.569
Weight (kg)	8.95±4.50	8.98±3.75	0.03	0.028	0.978

SD – Standard deviation

Table 2: Symptom-wise patient distribution

Symptoms	Frequency (%)		*P*
	Group 1 (*n*=30)	Group 2 (*n*=30)	
Dyspnoea	22 (73.3)	15 (50)	0.063
Diaphoresis	7 (23.3)	8 (26.7)	0.089
Poor sucking	9 (30)	10 (33.3)	0.077
Failure to thrive	11 (36.7)	18 (60)	0.071
Repeated chest infections	23 (76.7)	17 (56.7)	0.100

Table 3: Intraoperative time (cardiopulmonary bypass and aortic cross-clamp time) in both the groups

Intraoperative time	Mean±SD		Mean difference	*t*	*P*
	Group 1 (*n*=30)	Group 2 (*n*=30)			
CPB time (min)	100.76±15.59	96.8±14.95	−3.967	−1.005	0.319
Aortic cross-clamp time (min)	35.43±7.54	33.90±12.29	−1.533	−0.582	0.563

CPB – Cardiopulmonary bypass; SD – Standard deviation

Table 4: Pre-cardiopulmonary bypass variables in both the groups

Pre-CPB measurements	Mean±SD		*P*
	Group 1 (*n*=30)	Group 2 (*n*=30)	
PAP (mmHg)			
SBP	79.266±11.292	68.967±11.303	0.001
DBP	51.1±10.946	45.167±10.076	0.033
MAP	60.633±10.469	54.367±10.005	0.021
Systemic Intra-arterial pressure (mmHg)			
SBP	93.4±8.186	91.1±8.104	0.279
DBP	61±9.285	56.033±10.597	0.058
MAP	72.133±8.307	67.567±8.912	0.045
Pulmonary artery/aortic	0.838±0.093	0.802±0.105	0.166
SpO_2 (%)	98.933±1.201	98.567±1.223	0.246

CPB – Cardiopulmonary bypass; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MAP – Mean arterial pressure; SD – Standard deviation; PAP – Pulmonary artery pressure

Table 5: Post-cardiopulmonary bypass variables in both the groups

Post-CPB variables	Mean±SD		*P*
	Group 1 (*n*=30)	Group 2 (*n*=30)	
PAPs (mmHg)			
SBP	56.767±11.001	42.267±7.556	0.001
DBP	35.167±7.424	25.100±6.305	0.001
MAP	42.133±8.274	31.367±6.499	0.001
Intra-arterial pressures (mmHg)			
SBP	83.0±7.419	84.6±9.658	0.475
DBP	53.133±6.078	50.067±7.244	0.081
MAP	62.6±6.251	61.567±6.836	0.544
Pulmonary artery/aortic	0.677±0.112	0.508±0.101	0.001
Duration of ventilation (h)	28.067±15.422	23.233±13.868	0.207
ICU stay (h)	98.400±18.340	78.467±19.501	0.001

CPB – Cardiopulmonary bypass; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MAP – Mean arterial pressure; SD – Standard deviation; ICU – Intensive Care Unit; PAPs – Pulmonary artery pressures

and not barred of side effects. In contrast, sildenafil is available in oral forms, is well tolerated with no patient withdrawal and limited side effect profile.[10]

The study also aimed at evaluating mortality, morbidity and ICU stay in the two different groups.

Many studies have proved the effectiveness of sildenafil in the treatment of PAH of different aetiologies in adults. It lowers PAP and PVR, and it improves cardiac output, exercise tolerance and functional capacity.

The efficacy of sildenafil in controlling PAH in paediatric age group with CHDs was reported by many authors. Zeng *et al*.[11] determined a significant improvement in exercise capacity and pulmonary haemodynamics in terms of PVR and pulmonary blood flow in patients with PAH secondary to atrial septal defects, ventricular septal defects or patent ductus arteriosus. These findings were compatible with many other studies.[12,13]

Based on so many encouraging results, we began our study on two groups, sildenafil and control group in both preoperative and postoperative period in the Indian population. Because there is no recommended dose schedule in the paediatric age group, we based our doses on the current available literature.[10,14,15]

Both groups were similar in terms of clinical features, demographics, baseline pulmonary artery pressures, CPB time and aortic cross clamp time. El Midany *et al*. in 2013, while doing a similar study, found no significant difference in CPB and aortic cross-clamp time.[16]

The pre-CPB intra-arterial pressure difference between the two groups is statistically significant for the mean arterial pressure values. This is can be explained by the effect of sildenafil on systemic pressures where it can lead to some amount of hypotension as seen in another study, and also explains the use of pulmonary artery/aortic ratio for the comparison.[15]

Incidences of post-operative pulmonary hypertensive crisis were present but similar in both the groups. In Group 1, only one patient had three episodes of pulmonary artery hypertensive crisis whereas, in Group 2, two patients had two episodes each of pulmonary artery hypertensive crisis. Although the difference was not statistically significant, there were a fewer number of pulmonary hypertensive crisis episodes in sildenafil group. Chaudhari *et al*. reported a case in 2005 in which sildenafil helped in recovery from pulmonary hypertension crisis episode in a neonate with severe PAH. Long-term sildenafil also leads to complete resolution of PAH.[17]

No sepsis was reported in any of the patients in either of the two groups. Mortality difference in between the two groups was also not found significant.

In our study, difference of post-operative duration of ventilation in between the two groups remained statistically insignificant. However, post-operative ICU stay was significantly longer in Group 1 patients than in Group 2 patients. A similar study was performed by Palma *et al*. on 38 children with moderate-to-severe PAH who underwent cardiac surgery, and they

reported shortened CPB time, mechanical ventilation time and lengths of ICU and hospital stay.[18]

Our study has demonstrated a marked effect of pre- and post-operative sildenafil administration on mPAP as reflected by the progressive significant decrease of the mPAP from baseline to pre-CPB to post-CPB in both the groups. These results are similar to the study conducted by Nemoto *et al*., who demonstrated the efficacy of sildenafil in lowering pulmonary artery pressure and preventing crisis in the post-operative course after various types of congenital cardiac surgery.[19] Our study fills the gap in the current literature by adding more positive results of sildenafil in reducing pulmonary artery pressures effectively when used both pre- and post-operatively.

Evidence exists for the association between sildenafil and various systemic adverse effects, which have included the gastrointestinal, cardiovascular, visual and central nervous systems.[20] However, in our study, we did not encounter side effects of sildenafil therapy. Similar results were reported by many studies.[18,19]

Like all studies, our study also has some limitations that include relatively fewer patients, limited resources, no long term follow up and no PAP measurements in the postoperative period by echocardiography.

CONCLUSION

The use of perioperative sildenafil has a statistically significant reduction in the systolic pulmonary artery pressures and mean pulmonary artery pressure without any adverse effects.

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Conflicts of interest
There are no conflicts of interest.

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