Intravenous sildenafil for perioperative management of patients with pulmonary artery hypertension in congenital heart surgery – a prospective randomized study

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Background
In congenital heart disease (CHD), pulmonary artery hypertension is complicated by dysfunctional endogenous production of nitric oxide by pulmonary endothelium. Elevated activity of phosphodiesterase type 5 has also been demonstrated in such cases, and is amplified by cardiopulmonary bypass in postoperative children. Treatment with pulmonary vasodilators like milrinone, oral sildenafil, inhaled nitric oxide, and epoprostenol has been used with varying degrees of success. The current study aimed to investigate the efficacy and safety of intravenous sildenafil in postoperative children with increased pulmonary vascular resistance due to CHD.

Methodology and results
A prospective, randomized controlled trial was conducted in which 100 children of CHD with pulmonary artery hypertension were studied. All were randomly divided in two groups (S=sildenafil and C=control). Group-S patients received intravenous sildenafil (1.6 mg in 24 h), while in group C, similar amount of placebo (normal saline) infusion over 24 h started after removing aortic cross-clamp. In both the groups, the rest of the anesthetic and inotropic management was similar as per the institute's protocol. Intravenous sildenafil more effectively improved PO_2 : FiO_2 (P : F) ratio ($P<0.0001$), reduced pulmonary artery systolic pressure ($P<0.0001$), ventilation time (in h) (S=21.36±4.11, C=30.14±11.01, $P<0.0001$), length of ICU stay (in h) (S=68.74±10.11, C=87.56±27.78, $P<0.0001$), and length of hospital stay (in days) (S=10.5±1.23, C=12.46±1.99, $P<0.0001$).

Conclusion
Intravenous sildenafil is a safe and effective pulmonary vasodilator in the perioperative setting in children with CHD.

Keywords:
congenital heart disease, intravenous sildenafil, pulmonary hypertension

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Introduction

Pulmonary hypertension is defined as increase in mean pulmonary arterial pressure (mPAP) more than or equal to 25 mmHg at rest, as assessed by right-heart catheterization. It is commonly associated with left-to-right shunt defects leading to excessive pulmonary blood flow, or left-heart obstructive disease causing postcapillary pulmonary hypertension [1]. The risk of developing irreversible pulmonary vascular disease depends on the degree of pulmonary overcirculation, the pressure that the pulmonary arteries are exposed to, and the degree of hypoxia [1].

Pulmonary artery hypertension (PAH), if present, can be a significant cause of increased morbidity and mortality in children undergoing surgery for congenital heart diseases (CHD) [1]. Various techniques and drugs have been used for its management, including ventilation strategies directed toward adequate oxygenation and avoiding acidosis, as well as hypercarbia, adequate analgesia and sedation, and optimizing hematocrit [2]. The pharmacological management includes inhaled nitric oxide (iNO), phosphodiesterase (PDE) type-5 inhibitors (sildenafil), prostacyclin analogs (epoprostenol), endothelin-receptor antagonists (bosentan), and inodilators (milrinone) [2]. Among these, nitric oxide (NO) remains the treatment of choice [2], despite its shortcomings. However, some patients fail to respond to NO inhalation [3]. Alternatively responders to long-term NO therapy may develop severe, life-threatening rebound pulmonary hypertension on withdrawal of NO [4]. Recently, it

has been shown that by enhancement of the NO–arginine pathway, that is, by providing the substrate for NO production (L-arginine) and stimulating the enzyme responsible for NO formation (substance P), there is almost no pulmonary endothelial dysfunction in preoperative patients, and that it is possible to restore the pulmonary endothelial vasodilating function to a large degree in most postoperative patients [5].

Cyclic guanosine monophosphate (c-GMP) is produced by the interaction of NO with guanidine cyclase and is the final messenger for vascular smooth muscle relaxation. It is metabolized by a PDE-5, which is the predominant PDE in normal lung, and which may be upregulated in patients with primary pulmonary hypertension, and after cardiopulmonary bypass (CPB) [6], causing an increased turnover of c-GMP.

The inhibition of PDE-5 is therefore a logical step to increase the bioavailability of c-GMP and thus support endogenous vasodilation. Previous studies in animal models of pulmonary hypertension using the PDE inhibitors zaprinast or rolipram have confirmed this as a valid approach, but the data are less robust in humans treated with oral dipyridamole [7] and intravenous enoximone [8]. This is because both dipyridamole and enoximone have low sensitivity to the PDE-5 present in lungs, and their action is complicated by important systemic vasodilator effects.

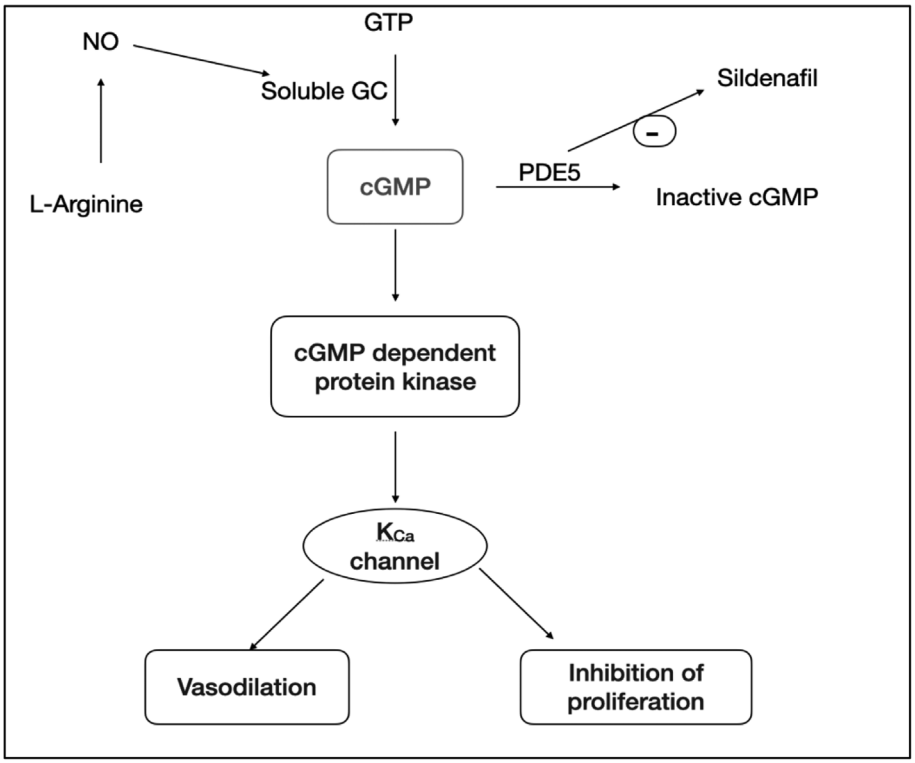
Sildenafil is a potent and selective inhibitor of c-GMP-specific PDE-5 (Fig. 1) [9]. The intravenous preparation of sildenafil makes it the only titrable PDE-5 inhibitor available so far. However, besides anecdotal reports from a few patients [10], there are no systematic data available on the effects of sildenafil in pulmonary circulation in children.

The purpose of this study was to evaluate the safety and efficacy of intravenous sildenafil in patients with moderate-to-severe pulmonary hypertension undergoing corrective surgery for CHDs [large ventricular septal defect (VSD), unobstructed total anomalous pulmonary venous connection (TAPVC)].

Materials and methods

This study was a double-blinded, prospective, randomized, single-center study conducted at a tertiary-level cardiac referral center after obtaining the approval from the ethical and the scientific committee of the institute and a written informed consent from the parents. From January 2017 to January 2019, 138 patients were screened, out of

Figure 1



Rationale for sildenafil use in PAH. GC, guanylate cyclase; GTP, guanosine triphosphate; PAH, pulmonary artery hypertension.

which 100 patients with weight more than 5 kg, belonging to American Society of Anesthesiologist's physical status II or III posted for surgical correction of VSD and unobstructed TAPVC, with proven PAH, that is, systolic PAP more than 35 mmHg or mPAP more than 25 mmHg, were included in the study. Patients with any genetic syndrome or ongoing inotropic or ventilatory support prior to surgery or allergy to study drug were excluded from the study (Fig. 2).

Operational definition

Pulmonary hypertensive crisis was diagnosed when any patient experienced pulse oximetry desaturation (<70%), hypotension (<60/30 mmHg), tachycardia followed by bradycardia (<30/min), and ST-segment changes on ECG in the postoperative period, in the absence of left-ventricular dysfunction by echocardiography.

Systemic hypotension (blood pressure is compared with the American Heart Association's fifth-percentile systolic blood pressures for age, which are as follows) [11]:

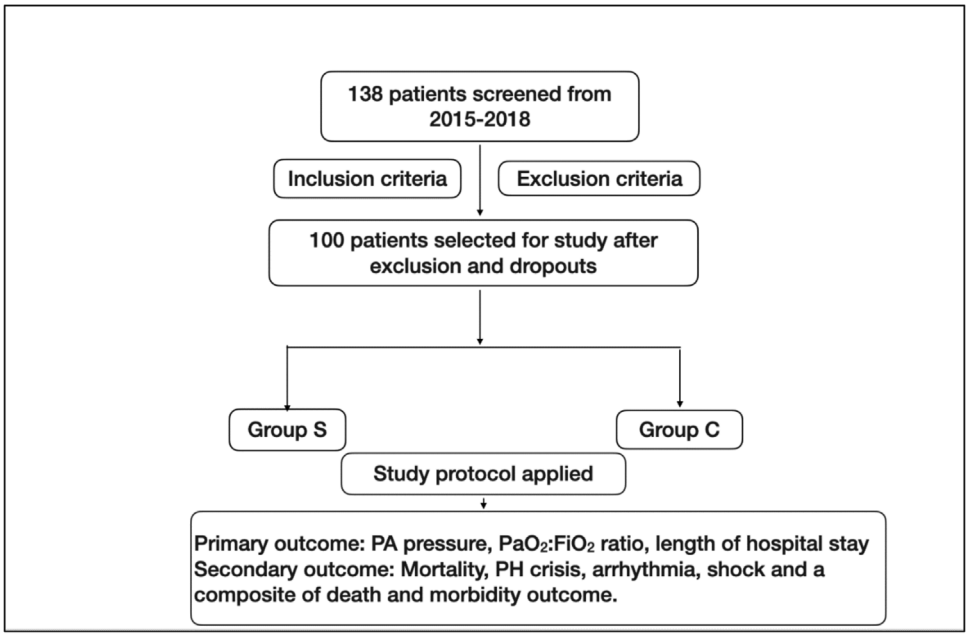
(1) Newborn: 60 mmHg.
(2) Infant (1 month to 1 year): 70 mmHg.
(3) Child (1–10 years): 70+(2×age [in years]) mmHg.

Hundred patients were equally allotted in two groups (S=sildenafil; C=control) using computer-generated random numbers. Patients were randomized sequentially one after another to either S or C groups. Group-S patients received intravenous sildenafil (1.6 mg in 24 h), while in group C, similar amount of placebo (normal saline) infusion over 24 h started after removing aortic cross-clamp .Oral sildenafil (0.5 mg/kg) was overlapped with termination of infusion. However, the rest of the anesthetic technique was the same for both the groups.

In the preoperative room, intranasal ketamine 1 mg/kg and nasal midazolam 0.4 mg/kg were given 15 min prior to induction. Anesthesia was given as per the institute's protocol. Standard monitoring, including five-lead ECG, pulse oximetry, end-tidal carbon dioxide monitoring, temperature monitoring (nasopharyngeal), with additional invasive monitoring, radial or femoral artery catheter, and a triple-lumen internal jugular or femoral central venous catheter. Induction of anesthesia was achieved with intravenous ketamine (1 mg/kg) with vecuronium (0.2 mg/kg). Anesthesia was maintained with 50% FiO_2 (air and oxygen mixture) and sevoflurane with 1–1.5 MAC, vecuronium (0.08 mg/kg), and fentanyl (2 μg/kg). Injection of dexmedetomidine 0.25 μg/kg/h was started after induction and continued throughout the perioperative period.

Ascending aortic and bicaval cannulation was performed after intravenous administration of 400 IU/kg unfractionated heparin and with an activated

Figure 2



Study design.

clotting time of more than 480 s. Surgery was performed on CPB with hypothermic cardiac arrest. After removal of aortic cross-clamp, standard inotropic supports were started in the form of 50 μg/kg milrinone loaded over 10 min followed by infusion of 0.5 μg/kg/min and infusion of adrenaline at 0.05–0.1 μg/kg/min.

Patients in group S received an initial loading dose of sildenafil 0.1 mg/kg/h for 4 h, followed by continuous infusion of intravenous sildenafil at 0.06 mg/kg/h in the postoperative period for the next 20 h (total 1.6 mg/kg over 24 h) [6]. Thereafter, tablet sildenafil 0.5 mg/kg twice daily was administered via nasogastric tube. Throughout the perioperative period, hematocrit was maintained around 30%. Patients were shifted intubated to the ICU. The rate of weaning of mechanical ventilation and the point of time of extubation were determined by the patient's hemodynamics and gas exchange, pattern of breathing, and daily radiographic findings. Sedation was not prolonged and extubation was not delayed for study reasons.

Patients in group C received similar amount of placebo (normal saline) infusion over 24 h that started after removing aortic cross-clamp. They received standard ICU care in the postoperative period, which included tablet sildenafil 0.5 mg/kg twice daily.

The additional inotrope/vasoconstrictor agents (inj adrenaline and inj milrinone infusion) were tapered once the patients were hemodynamically stable and showed no signs of tissue hypoperfusion as assessed by clinical signs and serial arterial and venous blood gases. Postoperative echocardiography was performed at regular intervals and at any particular instance where the patient showed major hemodynamic changes.

In our study, we had measured pulmonary artery systolic pressures (PASP) intraoperatively after the induction of anesthesia (at T1) using transesophageal echo (Philips, IE33, Netherlands) by measuring the maximum gradient of tricuspid-regurgitation jet (TR Gmax) and adding that value to the central venous pressure. Similar method was utilized to obtain the above values after coming off bypass (at T2). In the postoperative period, TR Gmax was obtained using transthoracic echocardiogram and the value was added to the central venous pressure to get the PASP at 12 h (T3), 24 h (T4), and 48 h (T5) after admission to the ICU. All patients underwent transthoracic echocardiography by the same, experienced pediatric echocardiographer who was blinded to the study group. All echocardiographic measurements were repeated thrice and then averaged.

The primary outcomes were heart rate, mean arterial blood pressure, PASP, PO_2 : FiO_2 ratio at various time intervals (T1=prebypass, T2=postbypass, T3=12 h after ICU admission, T4=24 h after ICU admission, and T5=48 h after ICU admission), CPB time, aortic cross-clamp time, ventilation time, and length of ICU and hospital stay. The secondary measured parameters were morbidity comprising of pulmonary hypertensive crisis, arrhythmia, systemic hypotension due to cardiogenic shock, and mortality. Collected data were analyzed using SPSS, version 20.0 software (SPSS Inc., Chicago, Illinois, USA). These data were presented as mean±SD or proportion as appropriate. The chi-square test was used to compare categorical and continuous variables, respectively. The *P* value less than 0.05 was considered to be significant.

Results

In total, 138 patients were enrolled in the study, out of which 100 patients were finally included after exclusion criteria and dropouts. They were randomized to one of the two groups: sildenafil (group S) or control (group C). The patient characteristics were similar between both the groups with respect to age, weight, height, BSA, sex, PASP (basal), and mean arterial pressure (MAP) (basal) (Tables 1 and 2).

Table 1 Demographic parameters

Parameters	Control (*N*=50)	Sildenafil (*N*=50)	*P* value
Age (months)	16.76±17.02	13.58±15.63	0.3330
Sex [*n* (%)]			
Male	22 (44)	19 (38)	0.6843
Female	28 (56)	31 (62)	
Height (cm)	67.5±9.92	64.55±9.59	0.2801
Weight (kg)	6.83±2.94	6.09±3.22	0.2330
Body surface area (m^2)	0.34±0.09	0.32±0.11	0.4761
Baseline PASP (mmHg)	61.1±8.61	60.8±9.55	0.8693
Baseline MAP (mmHg)	50.44±4.46	51.08±5.02	0.5021

MAP, mean arterial pressure; PASP, pulmonary artery systolic pressure.

Both the groups were comparable as far as the procedure performed on the study patients was concerned.

CPB time and cross-clamp time were not statistically different between the two groups as *P* value was more than 0.05. The mean time period for postoperative extubation in group S was 21.36±4.11 h, whereas that for group C was 30.14±11.01 h (Table 3). The postoperative ICU stay in group S was 68.74 ±10.11 h and in group C was 87.56±27.78 h (Table 3).

MAP (Table 4) and heart rate (Table 5) were comparable between the two groups at all time intervals.

The PO_2 : FiO_2 ratio (Table 6) was found to be comparable between the two groups at T1 and T2. However, the ratio was significantly lower in group C at T3, T4, and T5.

Comparison of PASP between the two groups at various time intervals (Table 7).

PASP were comparable between the two groups at T1 and T2, but PASP was significantly lower in the sildenafil group at T3 (12 h after admission to ICU) (C=33.24±1.7vs. S=25.9±2.77), T4 (24 h after admission to the ICU) (C=30.1±2.3 vs. S=21.5 ±2.19), and T5 (48 h after admission to the ICU) (C=25.3±1.3 vs. S=18.84±1.56).

Table 2 Type of surgery

Type of surgery	Control (*N*=50) [*n* (%)]	Sildenafil (*N*=50) [*n* (%)]	*P* value
VSD closure	43 (86)	41 (82)	0.785
VSD closure+PDA ligation	2 (4)	3 (6)	1.000
TAPVC repair	5 (10)	6 (12)	1.000

TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect.

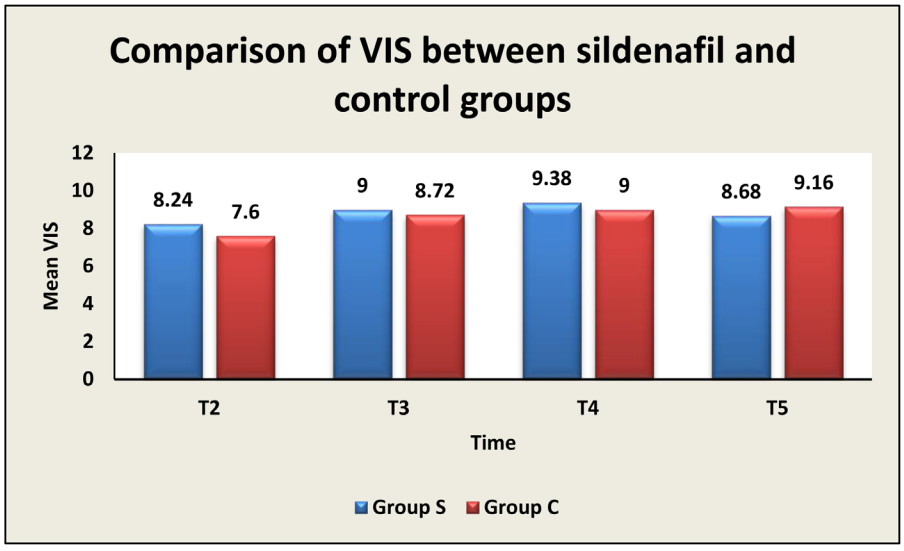
Table 3 Intraoperative and postoperative parameters

	Control (*N*=50)	Sildenafil (*N*=50)	*P* value
CPB time (min)	62.72±6.40	61.66±4.22	0.3312
Cross-clamp time (min)	43.64±7.6	41.74±3.13	0.1053
Ventilation time (h)	30.14±11.01	21.36±4.11	<0.0001
ICU stay (h)	87.56±27.78	68.74±10.11	<0.0001
Hospital stay (days)	12.46±1.99	10.5±1.23	<0.0001

CPB, cardiopulmonary bypass.

Table 4 Mean arterial pressure

Time	Control (*N*=50)	Sildenafil (*N*=50)	*P* value
T1	50.44±4.46	51.44±5.1	0.29
T2	44.46±3.81	45.22±4.02	0.33
T3	53.76±5.08	52.26±3.18	0.07
T4	58.28±4.18	57.14±4.26	0.179
T5	59.84±6.29	57.94±6.05	0.126



The graph showing the comparison of vasoactive inotropic score between two groups at various time points postoperatively (T2, T3, T4, and T5). Vasoactive inotropic score did not differ between the sildenafil and control groups.

Table 5 Mean heart rate

Time	Control (*N*=50)	Sildenafil (*N*=50)	*P* value
T1	135.44±13.43	135.98±11.95	0.8323
T2	149.16±7.568	148.68±7.71	0.7541
T3	136.36±7.93	135.96±8.76	0.8114
T4	128.78±9.62	128.56±9.76	0.9099
T5	123.5±9.40	122.56±9.16	0.6138

Table 6 Comparison of PO_2 : FiO_2 ratio between the two groups at various time intervals

Time	Control (*N*=50)	Sildenafil (*N*=50)	*P* value
T1	289.24±70.139	310.6±74.451	0.143
T2	211.64±30.687	217.96±30.369	0.303
T3	264.76±49.182	347.96±56.079	<0.0001
T4	272.48±40.676	410.26±41.606	<0.0001
T5	359.68±48.064	429.5±34.424	<0.0001

Table 7 Comparison of pulmonary artery systolic pressure

Time	Control (*N*=50)	Sildenafil (*N*=50)	*P* value
T1	61.1±8.61	60.8±9.55	0.8693
T2	35.76±4.30	35.02±4.15	0.3839
T3	33.24±1.7	25.9±2.77	<0.0001
T4	30.1±2.3	21.5±2.19	<0.0001
T5	25.3±1.3	18.84±1.56	<0.0001

Discussion

Children with many forms of CHD are prone to develop postoperative elevation in pulmonary vascular resistance [1]. The resultant pulmonary hypertension may complicate the postoperative course [2]. PAH may develop after CPB due to injury or transient dysfunction of the pulmonary endothelium [12], which may explain the limited efficacy of endothelium-dependent intravenous vasodilator therapy with nitroglycerine or prostaglandins [13]. Therefore, endothelium-independent pulmonary vasodilators may be indicated to treat persistent PH early after congenital surgery. At present, two such vasodilators are available: iNO and sildenafil.

Sildenafil has been shown to selectively reduce pulmonary vascular resistance. It produces vasodilatation by increasing c-GMP through inhibition of PDE-5, an enzyme that degrades c-GMP to guanosine monophosphate [14]. Sildenafil is an endothelium-independent pulmonary vasodilator, administered orally, is well tolerated with few drug interactions, and does not require intensive monitoring, all these making it a suitable drug for treatment of PH secondary to congenital heart defects. Also, malabsorption is common in critically ill patients and sometimes temporary occlusion of enteral feeding is required. Intravenous sildenafil may have an additional advantage in the management of PAH in the early postoperative period.

iNO, a selective pulmonary vasodilator, has been the therapy of choice for controlling PH after cardiac surgery. However, there are disadvantages with some of these therapies, including cost, technical complications, requirement of special delivery system, toxicity, etc. Life-threatening sequelae can occur when iNO is abruptly discontinued.

Most of the studies done exploring the therapeutic potential of sildenafil in pediatric cardiac surgeries have been conducted using oral sildenafil. Only a few studies substantiate the use of intravenous sildenafil. In a study by Stocker *et al.* [15], the combined effect of iNO and intravenous sildenafil was studied in 15 infants. The authors concluded that intravenous sildenafil augmented the pulmonary vasodilator effects of iNO in infants early after cardiac surgery. However, sildenafil produced systemic hypotension and impaired oxygenation, which was not improved by iNO.

In another study by Sharma *et al.* [16], the effect of intravenous sildenafil was studied in 43 patients undergoing corrective surgery for VSD with known pulmonary hypertension. The author concluded that intravenous sildenafil improves not only PaO_2 : FiO_2 ratio and PAP : AoP ratio (pulmonary artery and aortic pressure ratio), but also reduces extubation time and postoperative ICU. In another study by Fraisse *et al.* [17], which was a double-blinded, placebo-controlled study, it was concluded that intravenous sildenafil reduced pulmonary artery pressure and shortened the time to extubation and intensive care unit stay in children with postoperative PH. However, the study was heavily underpowered in which only 17 patients could be finally evaluated.

We began our study in two groups, sildenafil and control group in both the preoperative and postoperative period. Because there is no recommended dose schedule in the pediatric-age group, we based our doses on the current available literature [15,18]. Due stress was given on maintenance of adequate sedation and anesthesia right from the preoperative period in the form of nasal midazolam and ketamine, intraoperatively, with the use of intravenous dexmedetomidine and inhalational anesthetics, and postoperatively, by continuation of dexmedetomidine. Ventilation strategy was aimed to deliver adequate oxygenation, avoid acidosis, and hypercarbia. It was particularly ensured that suctioning is avoided in the lighter plane of anesthesia.

The present study has demonstrated a marked effect of sildenafil administration on PASP as reflected by the progressive significant decrease of the PASP from immediate post-CPB till discharge of patients in both groups. 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 both the preoperative period and postoperative period reduces pulmonary artery pressures much more than in patients where it is used in the postoperative period only.

In the present study, it was found that mean arterial pressures were reduced immediately after coming off bypass (T2) in both the groups and there was no significant difference between the two groups. While systemic hypotension may be of concern with sildenafil, it has been shown that the decrease in systemic blood pressure is seen when the drug given intravenously is clinically insignificant [19]. This could be partly explained by the use of adrenaline infusion (0.05–0.1 μg/kg/min), that is a part of the anesthetic protocol in our institute.

In a study by Sculze-Neick *et al.* [19], the effects of iNO (20 ppm) were compared before and after the stepwise infusion of sildenafil in 24 children and it was concluded that intravenous sildenafil is as effective as iNO as a pulmonary vasodilator in children with CHD. In this study, mean systemic blood pressure fell in response to the infusion of sildenafil (a fall of 7.3 ±2.5 mmHg, $P<0.01$), however, these changes in each patient remained clinically nonsignificant.

In the time periods T3, T4, and T5, there was no significant difference in the MAP between the two groups, which suggests that sildenafil does not cause any significant change in the systemic vascular resistance and systemic blood pressure.

In our study, we had measured PaO_2 : FiO_2 ratio from the blood gas analysis done at various predetermined time intervals to evaluate the adequacy of gas exchange, which might have been affected by pulmonary hypertension. We found that PaO_2 : FiO2 ratio at T1 (prebypass period) was comparable between the groups. However, it was found that this ratio was reduced in both the groups during the immediate postbypass period (T2), there was no statistical difference between the two groups. This reduction in the PaO_2 : FiO_2 ratio could possibly occur due to gas exchange affected in the immediate post-bypass period due to pulmonary endothelium dysfunction caused by CPB, increase in intrapulmonary shunt, some degree of pulmonary edema, and reduced pulmonary compliance caused by atelectasis due to nonventilation of lungs during the bypass period.

This ratio was found to be significantly lower in the control group in our study ($P<0.0001$) at T3, T4, and T5, which could be due to improvement in oxygenation as a result of decline in PAH. Similar result was found in the study by Sharma *et al.* [16] where pulmonary flow ratio was higher in group S.

We also found that the time required for weaning from ventilation and tracheal extubation was significantly lower in sildenafil group as compared with control group. Also, postoperative ICU stay was significantly less in sildenafil group than the control group.

A similar study was performed by Palma *et al.* [20] 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.

Despite the general management for reducing pulmonary hypertension, three of our patients develop pulmonary hypertensive crisis in the control group. In our study, we did not encounter the side effects of sildenafil therapy. Similar results were reported by Palma *et al.* [20] and Nemoto *et al* [21].

Our study is an attempt of filling the gap in the current literature by adding more positive results of sildenafil in reducing pulmonary artery pressures effectively when used both preoperatively and postoperatively.

In our study, none of the patients in either group had any major adverse event and there was also no mortality in either group of patients, suggesting the fact that intravenous infusion of sildenafil in the perioperative period is a safe and effective drug for the management of pulmonary hypertension.

Limitations

Small study population and heterogenous pathological conditions were few of the limitations of our study.

Conclusion

We have shown that perioperative administration of intravenous sildenafil reduces pulmonary artery pressures and improve PO_2 : FiO_2 ratio after surgical correction of CHDs (VSD and TAPVC), eventually leading to early weaning from mechanical ventilation, thus reducing the length of ICU stay.

It provides a well-tolerated, practical, and potentially effective treatment for PAH.

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Conflicts of interest

There are no conflicts of interest.

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