Journal of Clinical & Experimental Cardiology

Hofer et al., J Clin Exp Cardiolog 2015, 6:8
DOI: 10.4172/2155-9880.1000392

Research Article Open Access

A Prospective Randomised Study of Postoperative Prophylactic Application of Sildenafil After Pediatric Cardiac Surgery

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Received date: Jul 13, 2015; **Accepted date:** Aug 10 2015; **Published date:** Aug 17 2015

Abstract

Postoperative aggravation of pulmonary hypertension after pediatric cardiac surgery due to temporary endothelial dysfunction may lead to sudden pulmonary arterial pressure rise with compromise of right ventricular function. Though treatment with inhaled nitric oxid (NO) has been successful, rebound pulmonary hypertension has been observed after NO withdrawal due to supression of endogenous NO sythase. Sildenafil has been shown to prevent this reaction and is widely used after pediatric cardiac surgery. The aim of our study was to evaluate the effectively of postoperative administration of oral sildenafil (1 mg/kg/day) in preventing postoperative pulmonary hypertensive crises. 21 patients after repair of complete atrioventricular canal (n=10) or ventricular septal defect (n=11) were randomly assigned to the study group or control group. The study group received sildenafil after surgery via nasogastric tube every eight hours for 48 hours, the control group received placebo. The primary outcome parameter was the number of pulmonary hypertensive events (spontaneous pulmonary arterial pressure rise to or above systemic arterial pressure). Secondary outcome parameters were: need for inotropic drugs, fluid balance, urinary output, days on the ventilator or in the intensive care unit (ICU). There was no difference in the number of pulmonary hypertensive events between both groups: median (IQR); 2 (0-6,5) sildenafil, 1 (0-2) placebo, p=0,67. Neither inotrope score, time on the ventilator, ICU length of stay, nor fluid balance differed significantly. Urinary output was significantly lower in the sildenafil group.

Keywords: Congenital heart defects; Pulmonary hypertension; Pediatric intensive care units; Sildenafil; Nitric oxide synthase; Cardiopulmonary bypass

Introduction

Congenital heart defects with intracardial left to right shunting are often associated with elevated pulmonary vascular resistance [1,2]. Corrective surgery at an early age reduces the incidence of postoperative pulmonary arterial pressure rise. However pulmonary hypertension often deteriorates after cardiopulmonary bypass due to temporary endothelial dysfunction and suppression of endogenous nitric oxide (NO) production. This will result in a decline of the synthesis of cyclic guanosine monophosphate (cGMP), a key player in the regulation of pulmonary vascular reactivity. Furthermore systemic inflammatory response syndrome associated with cardiopulmonary bypass regularly triggers an increase of endothelin levels, resulting in intensified pulmonary vasoconstriction. As a consequence patients born with complete atrioventricular canal (CAVC) or large ventricular septal defects (VSD) are at increased risk of postoperative pulmonary hypertensive crises with subsequent right heart failure. Among those, patients with Down syndrome have even higher plasma endothelin levels pre-and postoperatively and there is a correlation between preoperative pulmonary to systemic pressure ratio and endothelin concentration before and after cardiopulmonary bypass in Down and non-Down children [3]. Postoperative recovery may thus be delayed as a function of pulmonary hypertension.

Though the individual response may vary among patients, therapy with inhaled NO has been shown to be effective [4,5]. But administration of exogenous NO may also result in down-regulation of NO synthase. Therefore rebound pulmonary hypertension can occur during weaning of inhaled NO. In order to prevent this reaction the phosphodiesterase 5 inhibitor sildenafil is widely used to facilitate NO withdrawal [6,7]. Phophodiesterase type 5 (PDE5) is highly expressed in pulmonary vascular smooth muscles and is responsible for the breakdown of cGMP. By inhibiting this pathway cGMP levels are maintained during sudden NO termination. Subsequently sildenafil has been used after pediatric cardiac surgery together with inhaled NO and bosentan [8]. The medication was also well tolerated among children with idiopathic pulmonary hypertension [9-11].

It has been demonstrated, that beyond the therapeutic use of sildenafil a prophylactic strategy is effective in the prevention of pulmonary hypertensive crises. This approach includes the application of sildenafil several days before cardiac surgery. However this strategy yields one major disadvantage. Preoperative application of sildenafil has the potential to increase the amount of blood shunted from the left to the right heart. As a consequence, theoretically pulmonary hyper perfusion might occur with the danger of deterioration of pulmonary function and myocardial performance before cardiac surgery. This might even reduce the chances of success of the procedure. Therefore it was the aim of this pilot study to investigate whether postoperative prophylactic application of sildenafil is as effective in preventing pulmonary hypertensive crises. This approach could effectively circumvent the dangers of preoperative application described above.

However, up to now no study has been published, that investigates the effect of sildenafil on the prevention of pulmonary hypertensive crises in younger children. We therefore investigated the effect of a prophylactic administration of sildenafil in the postoperative period on the occurrence of pulmonary hypertensive crises.

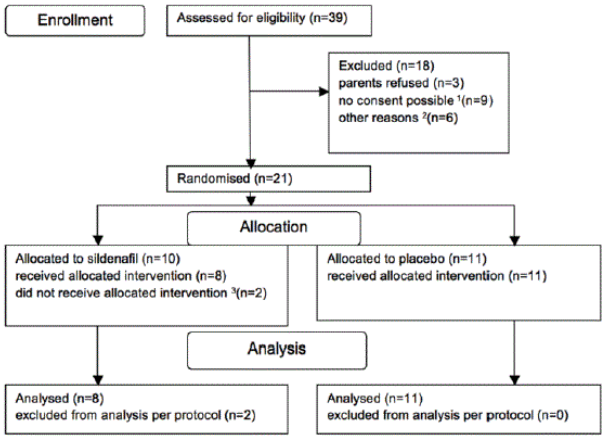

Figure 1: Consort flow chart of enrollment characteristics. 1- In 9 children consent could not be obtained because of language problems or absent legal representative. 2- Other reasons: One child's operation was cancelled, one child suffered from cerebral ischemia preoperatively, 4 patients were not included due to lack of resources of staff. 3- 2 patients did not receive intervention because of left ventricular failure and parental consent withdrawal respectively. n: number of patients.

Materials and Methods

Between March 2012 and March 2014, 21 out of 39 eligible patients between 1.5 and 6.5 months of age were enrolled in a prospective, single centre double-blind trial by the study team. Inclusion criteria were children with either ventricular septal defect (VSD) or complete atrioventricular canal (CAVC) and pulmonary hypertension. Pulmonary hypertension was assessed by echocardiography only. In all cases there was a large nonrestrictive VSD with bidirectional shunting, indicating systemic right ventricular pressures. None of the children had infundibular, valvular, or peripheral pulmonary artery stenosis. Exclusion criteria were: structural abnormalities of the left ventricle (mitral stenosis, endocard fibroelastosis, left ventricular failure) influencing pulmonary vascular resistance, postoperative residual VSD, children on the ventilator preoperatively, cardiogenic shock, extracorporeal membrane oxygenation, dialysis and absent parental consent.

Ethical approval for this study was provided by the Ethical Committee of Upper Austria, Linz, and parental informed consent was obtained for each patient. All patients had a correction of their congenital heart defect on cardiopulmonary bypass.

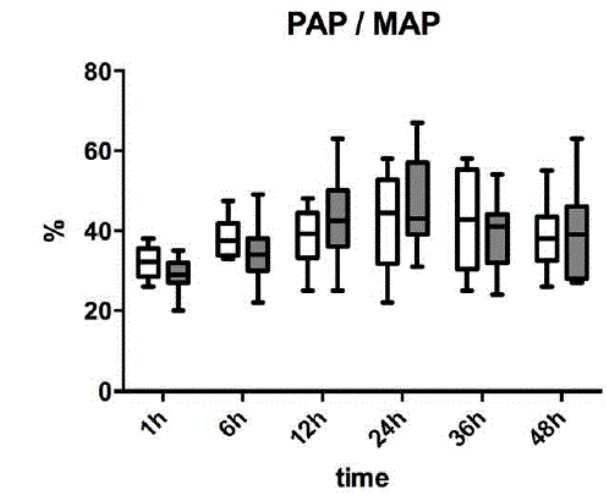

Figure 2: Time course of mean PAP-mean pulmonary arterial pressure as a fraction of MAP-mean arterial pressure; white bars: sildenafil, dark bars: placebo.

The patients were allocated to treatment or placebo using a computer generated randomisation plan in blocks of four. The study medication was prepared at the hospital´s pharmacy in 6 syringes for every patient after participants had been allocated to treatment or placebo. Sildenafil (Revatio®, Pfizer, Austria) was dissolved in an opaque solution (OraSweet® and OraPlus®, Paddock Laboratories, USA) and stored at 4°C until instillation. Placebo consisted of the same opaque solution of Orasweet® and Oraplus®. Therefore physicians, nurses and parents were unaware of the study group assignments. A blinding envelope was added to every study medication, which theoretically allowed unbinding in case of an emergency.

VSDs were closed using a pericardial patch, CAVC correction was performed by the single patch technique, attachment of the bridging leaflets and suture of the mitral valve cleft. A balanced anaesthesia technique was applied, by using midazolam, thiopental, sufentanil and cisatracurium. A central venous line was inserted into the right internal jugular vein and an arterial line into the right radial artery after induction of anaesthesia. Sevofluran was added to the inspiratory limb of the ventilator or the oxygenator of cardiopulmonary bypass. After corrective surgery on cardiopulmonary bypass (moderate hypothermia: 28-30°C, alpha-stat, minimum hematocrit 25%) the patients were transferred to our pediatric cardiac ICU, still sedated, ventilated, and on inotropic support as needed. Pressure lines were inserted into the pulmonary artery and into the left atrium by the surgeon at the end of surgery. A transthoracic echocardiography and shunt evaluation were performed after admission to rule out any residual VSD or relevant mitral regurgitation before starting the study protocol. The treatment group received Sildenafil via a nasogastric tube (1 mg/kg/day divided into 3 doses, starting 1 hour after ICU admission) for 48 hours. Besides echocardiography, adjustment of catecholamines, sedation and ventilation could be performed during this short delay. The control group received placebo via nasogastric tube every eight hours for 48 hours.

Sedation was continued for 24 hours by continuous infusion of midazolam and piritramid and ventilation was performed by a pressure controlled mode. FiO_2 was adjusted to keep arterial oxygen saturation above 97%. Hypercarbia as a trigger of pulmonary arterial pressure rise was also avoided by keeping $paCO_2$ between 35 and 45 mmHg. Therefore tidal volume at the ventilator was closely observed and measures (suctioning, recruitment) were taken in case of decreasing tidal volume to prevent hypercarbia. To avoid any influence of pH on pulmonary hypertension pH was kept between 7.35 and 7.45 during the study period by adapted infusion of $NaHCO_3$. Pulmonary arterial pressure increase was treated according to our routine practice by hyperventilation with pure oxygen, deepening of sedation, and muscle relaxation if needed. According to the study protocol inhaled NO was only allowed in the case of failing conservative treatment mentioned above and could be avoided in all cases. After the 24 hour sedation period Sildenafil was given in case of pulmonary hypertensive crisis up to 1 mg/kg/day in both groups, ensuring a maximum dosage of 2 mg/kg/day for the treatment group.

During the first 48 hours after ICU admission sytemic blood pressure, pulmonary arterial pressure, central venous pressure, left atrial pressure were recorded continuously. Cardiac output was measured continuously by pulse contour analysis (LIDCOrapid®, Lidco limited London). Arterial and a mixed venous blood samples were drawn 1, 6, 12, 24, 36 and 48 hours after admission to measure arterial and mixed venous oxygen saturation and lactate concentration.

As primary outcome parameter a rise of pulmonary arterial pressure equal to or greater than systemic pressure was recorded at the time of occurrence.

	Sildenafil	Placebo	p
Age; months, median (interquartile range)	3.25 (3-4)	4 (3-5)	0.73
Weight, kg; mean ± SD	4.48 ± 0.82	4.8 ± 1.01	0.48
Male sex; n (%)	5 (45)	6 (75)	0.35
VSD; n (%)	6 (75)	5 (45)	0.35
Down; n (%)	5 (63)	8 (64)	1
Diuretic therapy; n (%)	3 (38)	6 (55)	0.65
Cardiopulmonary bypass time (min); mean ± SD	111.4 ± 27.57	131.5 ± 40.23	0.24

Table 1: Baseline characteristics and cardiopulmonary bypass time.

Second outcome parameters were mean pulmonary arterial blood pressure as percentage of mean arterial blood pressure measured at 1, 6, 12, 24, 36 and 48 hours after ICU admission. Furthermore the inotrope score was calculated according to standard formula (dobutamine [µg/kg/min]+milrinon[µg/kg/min] × 10+(nor-) epinephrine [µg/kg/min] × 100) [12,13]. Fluid demand and urinary output were recorded after 24 and 48 hours. Days on the ventilator and ICU stay were compared between groups.

Statistical analysis: Since not all parameters obtained were normally distributed descriptive statistics were calculated as median ± interquartile range. Differences between groups of parameters that have been collected only once were tested by a student's t test or a Mann Whitney U test as appropriate. For all other parameters with multiple collections during the course of the study either a 2-way repeated measurement ANOVA or an ANOVA on ranks was performed as appropriate.

Results

Between March 2011 and March 2013, 21 patients were randomised. Two patients of the sildenafil group were excluded after randomisation because of left ventricular failure and withdrawal of parental consent respectively. 8 children remained in the sildenafil and 11 children in the placebo group. All patients entering analysis were treated according to the study protocol (Figure 1).

There was no statistical difference concerning base line parameters of both study cohorts as well as no difference between times on cardiopulmonary bypass (Table1).

Pulmonary hypertensive events

There was no difference between the two study groups in the main outcome parameter: sudden pulmonary arterial pressure increase equal to or above systemic arterial pressure, 2 (0-6.5) in the sildenafil group, 1 (0-2) in the placebo group, median (interquartile range), p=0.67.

Secondary outcome parameters

Need of catecholamines measured by the inotrope score was not different between groups. Both groups had similar time on the ventilator and ICU length of stay. Urine output was significantly lower in the sildenafil group during the first and the second postoperative day. This is possibly consistent with sildenafil induced fluid retention. However this finding did not influence fluid balance after 24 or 48 hours, which was not different between both groups (Table 2).

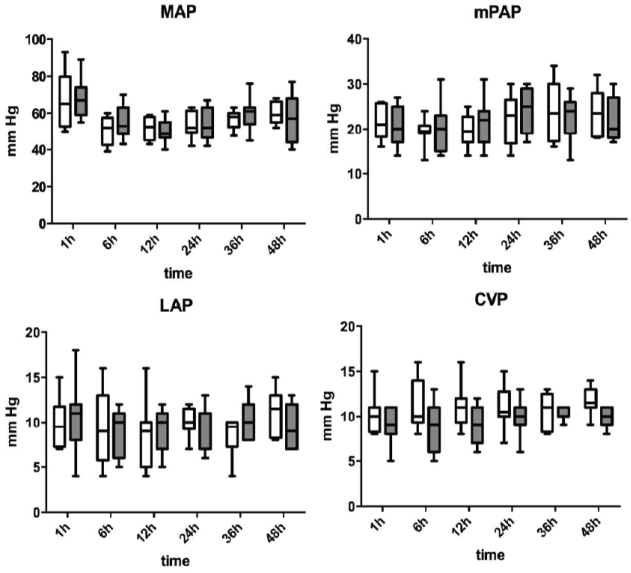

Figure 3: Time course of mean arterial pressure (MAP), mean pulmonary arterial pressure (mPAP), left atrial pressure (LAP), central venous pressure (CVP); white bars: sildenafil, dark bars: placebo.

Variable	Sildenafil	Placebo	p
Number of pulmonary hypertensive events, median (interquartile range)	2 (0-6.5)	1 (0-3)	0.67
Inotrope score, median (interquartile range)	6 (3.5-12.94)	9.5 (5-12)	0.56
Mechanical ventilation, hours; median (interquartile range)	77 (58-09.3)	57 (53-144)	0.68
Intensive care unit length of stay, days; median (interquartile range)	7.25 (6-8)	5 (4-9)	0.24
Fluid day 1, ml/kg; median (interquartile range)	83 (68-114)	71 (61-89)	0.54
Fluid day 2, ml/kg; median (interquartile range)	-8 (-20 ± 35)	-1 (-31 ± 11)	0.65
Urine output day 1, ml/kg; median (interquartile range)	30 (23-39)	45 (41-51)	0.04
Urine output day 2, ml/kg; median (interquartile range)	83 (42-103)	111 (93-124)	0.014

Table 2: Primary and secondary outcome parameters.

Hemodynamic measurements

No difference for the mean PAP/MAP ratio was observed during the study period between both groups. (p=0.95) However the ratio increased over time as a sign for different levels of sedation (Figure 2). Mean systemic arterial pressure (MAP) decreased during the first 6 hours after admission, possibly due to systemic inflammatory reaction in both groups with no difference between the groups (p=0.9) and was stable thereafter. There was also no difference in left atrial pressure (LAP) (p=0.85) and mean pulmonary arterial pressure p=0.99. Central venous pressure (CVP) was slightly higher in sildenafil treated patients at all measurement points p=0.048, but there was no difference in postoperative right ventricular function assessed by routine echocardiography (Figure 3). No difference was detected for Cardiac index (p=0.16), SvO_2 (p=0.37) and arterial lactate (p=0.64) between both groups during the 48 hours observation period (Figure 4).

There was no death in our study. Two patients had to be reintubated due to atelectases (sildenafil group) and opioid over dosage (placebo group) respectively. 4 patients had pericardial effusion (3 sildenafil, 1 placebo), 2 patients had pleural effusion (1 sildenafil, 1 placebo) and 1 patient suffered from chylothorax after starting enteral nutrition (sildenafil). 2 patients of the placebo group were treated with levosimendan due to worsening cardiac function. All adverse events (except one pericardial effusion in the sildenafil group) occurred after the study period.

Discussion

Application of the PDE 5 inhibitor sildenafil directly after ICU admission was expected to prevent spontaneous postoperative pulmonary arterial pressure rise in children with an extended risk profile, especially patients with large VSDs or CAVC. Absolute values of pulmonary arterial pressure can only be measured by cardiac catheterisation, and echocardiography is recommended as a non-invasive modality for screening PAH [14]. A good correlation between right ventricular systolic pressure estimated by echocardiography and systolic pulmonary arterial pressure measured by right heart catheterisation has been found in children with congenital heart disease [15]. Though we did not measure pulmonary vascular resistance in the catheter laboratory preoperatively, it is known that systemic pulmonary artery pressures lead to morphologic changes of the pulmonary arteries thus increasing the risk for postoperative pulmonary hypertensive crises.

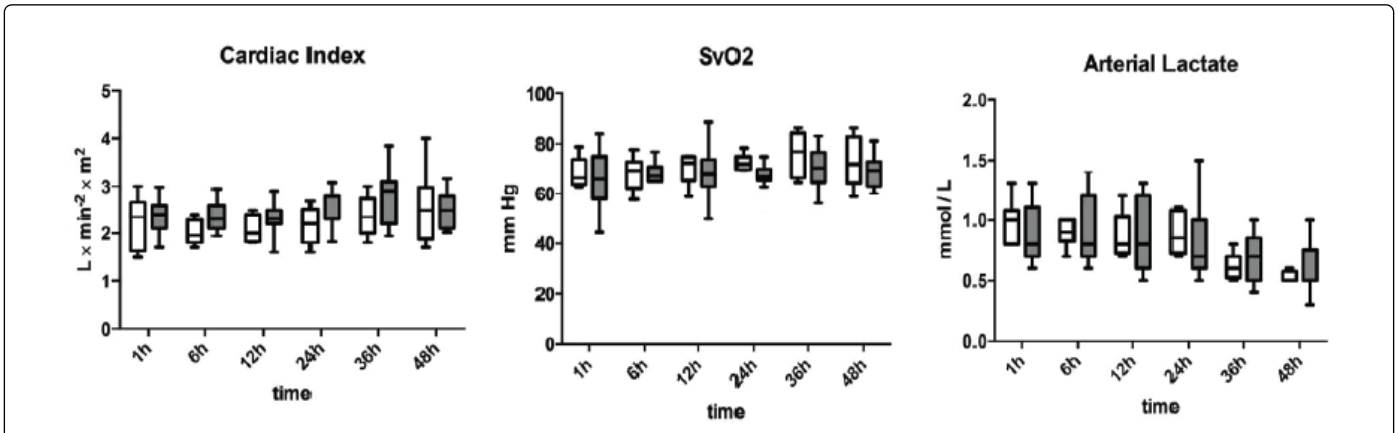

Figure 4: Time course of cardiac index (CI), mixed venous oxygen saturation (SvO_2) and arterial lactate; white bars: sildenafil, dark bars: placebo.

In addition shortening of postoperative recovery in terms of time on the ventilator and ICU stay was anticipated. In contrast to some other data, our pilot study did not show a benefit of giving sildenafil prophylactically. Several studies have been conducted with different application schedules that demonstrated variable degrees of efficacy and clinical outcome.

Palma et al. showed in a retrospective study in VSD patients, that application of sildenafil 1 week before and 1 week after the surgical procedure significantly lowered pulmonary arterial pressure and pulmonary/systemic pressure ratios in contrast to patients who received sildenafil solely in the postoperative period. In addition a preventive application scheme avoided pulmonary hypertensive crises [16]. However, preoperative treatment of patients with sildenafil is not without danger. The existing left to right shunt could increase

extensively and provoke heart failure. Moreover a residual VSD after operation is usually defined a contraindication for sildenafil treatment at our institution. Therefore we performed transthoracic echocardiography to rule out any significant residual VSD before starting the study protocol. Another reason for not initiating sildenafil before the operation is the unknown influence of cardiopulmonary bypass on sildenafil pharmacokinetics. We also refrained from giving sildenafil in the operating room postoperatively because of insecure enteral resorption and potential hemodynamic effects immediately after bypass.

In contrast to the results of Palma two other studies could not confirm the superiority of preoperative sildenafil administration. In the first study treatment with oral sildenafil two weeks prior to surgery was not superior to postoperative therapy in reducing mean pulmonary arterial pressure in a randomised controlled trial of VSD patients [17]. Nevertheless patients treated with sildenafil preoperatively had a shorter ICU stay. The same result was obtained in a randomised trial when sildenafil was administered 24 to 8 hours before surgery [18]. No difference in the reduction of postoperative pulmonary arterial resistance could be observed. Pre-and postoperative cGMP levels and NO breakdown products as a surrogate of endothelial function were not statistically different. But interestingly the patients treated with sildenafil had a more restricted postoperative biventricular cardiac function assessed by echocardiography, possibly through inhibition of cyclic adenosine monophosphate (cAMP) by cGMP, reduced myocardial calcium sensitivity and blunted response to adrenergic stimuli. In addition a reduction in oxygen delivery was found. The authors adviced against the routine use of sildenafil in patients with pre-existing hypoxia or myocardial dysfunction.

Our result might also have been influenced by the fact that the dosage applied was rather low. Moreover, diminished visceral blood flow and gastrointestinal motility due to the postoperative use of opioids could have reduced bioavailability of the drug. Nevertheless, in a prospective observational study 0.5 mg/kg every four hours was as effective as 2 mg/kg, when given along with nitric oxide. But with the higher dosage, arterial oxygen partial pressure decreased due to intrapulmonary shunt [19]. To overcome the problems with enteral resorption intravenous sildenafil might have been an alternative. However, i.v. sildenafil was not available in our country at initiation of the study protocol. In addition also i.v. sildenafil has been shown to induce ventilation-perfusion mismatch by acting throughout the pulmonary vasculature [20,21].

Sildenafil therapy was continued according to the course of pulmonary arterial pressure only in eight of our nineteen patients. This therapy was well tolerated. Taking into account the oxygenation parameters of the verum group it has to be stated that we did not observe any signs of increased intrapulmonary shunting with consecutive tissue hypoxia. Furthermore repeated TTE controls did not show worsening cardiac function in the sildenafil group. Nevertheless eight patients of the control group (5 VSD, 3 CAVC) did not receive sildenafil treatment throughout the whole study period and thereafter. Accordingly a substantial proportion of our patients would have been treated inadvertently by giving sildenafil prophylactically.

One major drawback of our study might be the low number of patients included. The study presented had been designed as a pilot study, and therefore it cannot be excluded, that small, statistically insignificant, but clinically relevant results have been missed. However, our data suggest that the number of patients needed to find any difference between our two study groups is too high to justify a larger randomised single center study.

Conclusion

Postoperative prophylactic administration of sildenafil could not influence the clinical course after VSD or CAVC correction in our small patient cohort, especially sudden increases in pulmonary arterial pressure. As the medication may at least theoretically worsen oxygenation and myocardial function after cardiac surgery, reasonable use in children with pulmonary arterial hypertension after cardiac surgery is advised.

Acknowledgment

We want to thank Dr. Pointinger from the hospital pharmacy for her valuable contribution concerning the preparation of the study medication and the colleagues involved in the postoperative care of our patients.

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