

First experience with sildenafil after Fontan operation: short-term outcomes

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Background We conducted a retrospective study to determine the effect of oral sildenafil administered as monotherapy after Fontan operation in single ventricle physiology.

Methods From January 2008 to March 2012, during two different periods, a total of 30 pediatric patients undergoing Fontan operation by extracardiac conduit were included in this study. Thirteen patients were in the sildenafil group and exclusively treated with sildenafil given at the dose of 0.35 mg/kg through a nasogastric tube and then orally every 4 h, at the start of cardiopulmonary bypass and for the first postoperative week; then we reduced and discontinued the therapy. The other 17 patients were in the control group. No other vasodilator was administered in both groups. We analyzed intraoperative and postoperative outcomes of sildenafil administration.

Results There were no differences in mortality or operative time. The total and relative drainage loss was lower in the sildenafil group ($P=0.0003$ and 0.0045). The hemodynamic parameters showed a better condition in the sildenafil group, with a lower mean pulmonary artery pressure (mPAP) ($P=0.0001$) and better mPAP to mean systemic

blood pressure (mSBP) ratio ($P=0.0043$), whereas there was no difference in peripheral oxygen saturation ($P=0.31$). The sildenafil group patients showed other additional positive differences as well as lower inotropic score ($P=0.0005$) and intubation time ($P=0.0004$). No complications related to the use of sildenafil were noted in any of the children studied.

Conclusion This initial experience provides evidence that sildenafil may be used in postoperative Fontan operation with positive effectiveness.

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Introduction

Although the use of sildenafil has become a standard therapy for adults with pulmonary hypertension, clinical reports pertaining to the use of oral sildenafil therapy (OST) (Viagra; Pfizer laboratory, New York, USA) in the pediatric population with congenital heart disease (CHD) have appeared only in recent years.^{1–3} Because of the diversity of the hemodynamic features in patients with CHD, it may be difficult to determine the efficacy of OST in this patient population.

Sildenafil is a selective phosphodiesterase V (PDE V) inhibitor.¹ PDE V specifically hydrolyzes guanosine 3',5'-cyclic monophosphate (cGMP).

Very important to the success of patients undergoing Fontan staging is the low pulmonary vascular resistance (PVR). Persistent pleural effusions, protein-losing enteropathy, formation of collateral vessels, excessive cyanosis, and failure to thrive are a few of the complications in this patient population. The acute use of nitric oxide and other pulmonary vasodilators has been

reported for single ventricle (patients with Fontan physiology and low cardiac output associated with high pulmonary artery pressures).⁴ However, some patients become symptomatic months to years after Fontan surgery, and with continued evidence of failure of the circulation, they are eventually referred for cardiac transplantation.

We conducted a retrospective study to determine the effect of oral sildenafil administered as monotherapy after Fontan operation in single ventricle physiology.

Material and methods

Patient selection

The data used in this retrospective study were collected at our center during two different periods. Approval was gained from the Ethics Committee of the University of Naples Federico II. The Institutional Review Board had approved the use of databases for research. All participants were younger than 18 years of age and each legal

guardian had preliminarily granted permission for the use of their medical records for research purposes.

Children who were scheduled to undergo Fontan operation between January 2008 and March 2012 were considered potentially eligible for inclusion in the study. Regarding the surgical technique employed for the Fontan operation, extracardiac conduit connection between the inferior vena cava and the pulmonary artery was performed in all patients. No fenestration of Fontan pathway was performed.

The control group included patients who underwent surgery between January 2008 and December 2009. During this period no OST was used. The sildenafil group included all children undergoing Fontan operation between January 2010 and March 2012. In this group, sildenafil was administered at the dose of 0.35 mg/kg through a nasogastric tube and then orally every 4h. We started the first dose of treatment at the beginning of cardiopulmonary bypass (CPB), continuing for the first postoperative week; then we reduced and discontinued therapy.

In both groups, preoperative catheterization showed low pulmonary artery pressure (below 15 mmHg) and pulmonary vascular resistance less than 2.5 Wood units.^{4,5}

Perioperative management of patients

All other parameters that may influence the perioperative management, in particular anesthesia, CPB course and extubation protocol, were not modified during the two periods under review. All patients were operated upon by a surgical team of two surgeons without surgical practice difference between the two time periods. The following hemodynamic parameters were measured immediately after surgery and for a further 72h: mean pulmonary artery pressure (mPAP), the ratio of mPAP to mean

systemic blood pressure (mPAP/mSBP), and peripheral oxygen saturation (SpO₂) were measured every 3 h after the first administration of OST via invasive systemic arterial and pulmonary arterial lines. Blood and fluid loss via drains was defined as the total amount lost via thoracic drains after surgery until their removal. We removed thoracic drains when fluid loss was less more 3 ml/kg per day. The anesthesiologists were responsible for intraoperative fluid management. We recorded the total time of surgery and the CPB.

Postoperatively, patients were transferred to the ICU. In addition to sildenafil, therapy included administering 1–15 µg/kg per min of dopamine or dobutamine (0.05–0.2 µg/kg per min of adrenaline was added, when necessary), 0.075–0.15 µg/kg per min of remifentanyl, and 0.5–2 µg/kg per min of midazolam for sedation. Controlled ventilation was instituted in order to attain blood pH values above 7.45 and PaO₂ levels above 100 mmHg. Postoperative care was undertaken by a team of intensivists who managed bleeding and blood product administration according to existing protocols. Packed red cells were used for transfusion if the hemoglobin fell below 11 g/dl, although a clear-cut trigger of transfusion was not defined in this study. Fresh frozen plasma was used if the hemoglobin was above 11 g/dl and the patients' clotting factors were considered based on the results of coagulation tests. Platelet concentrates were used in a dose of 1 unit (50 ml) per 10 kg, and 5% albumin was used for volume replacement if no active bleeding was present. We performed a replacement of losses by thoracic drainage following the replacement/loss ratio as 1:1 for the first 2 days after surgery, 1:2 ratio for the next 3 days, and 1:4 ratio up to the removal of the drainage. Then we recorded the intubation time, ICU stay, and the inotropic score was calculated as dopamine µg/kg/min × 1 + dobutamine µg/kg/min ×

Table 1 Demographic and preoperative data between sildenafil and control group

Characteristics of patients	Sildenafil group (n = 13)	Control group (n = 17)	P value
Age (months)	55 ± 12	59 ± 14	0.42
Sex (male)	8 (61%)	10 (59%)	0.82
Weight (kg)	19.7 ± 3.1	21.1 ± 4.1	0.31
BSA (m ²)	0.77 ± 0.09	0.82 ± 0.12	0.22
mPAP (mmHg)	12.1 ± 0.6	11.8 ± 0.8	0.27
mPAP/mSBP	0.22 ± 0.02	0.21 ± 0.04	0.42
SpO ₂ (%)	82.5 ± 1.7	84.1 ± 2.5	0.06
PVR (Wood units)	2.2 ± 0.2	2.1 ± 0.3	0.30
PCWP (mmHg)	8.9 ± 0.6	9.2 ± 1.0	0.34
Hemoglobin (g/dl)	15.5 ± 1.4	15.2 ± 1.1	0.51
Creatinine (mg/dl)	0.6 ± 0.2	0.7 ± 0.2	0.18
Intracardiac defects			
TA	4	5	0.62
Univentricular heart	4	4	0.52
TGV + PS + strad AVV	0	1	0.58
AVSD unbalanced	4	6	0.57
HLHS	0	1	0.58

AVSD, atrioventricular septal defect; BSA, body surface area; HLHS, hypoplastic left heart syndrome; mPAP, mean pulmonary artery pressure; mSBP, mean systemic blood pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SpO₂, peripheral oxygen saturation; TA, tricuspid atresia; TGV + PS + strad AVV, transposition of the great vessels, pulmonary stenosis, straddling atrioventricular valve.

1 + epinephrine $\mu\text{g}/\text{kg}/\text{min} \times 100$.⁶ Diuretics (usually furosemide 1–2 mg/kg per dose, two to four times daily) were begun on the first postoperative morning or earlier if the patient was oliguric (less than 1 ml/kg per h).

Statistical analyses

Continuous data are presented as mean \pm SD. We compared clinical variables between the two groups by means of the nonparametric Mann–Whitney *U* test (for continuous variables) or the χ^2 test and Fisher's exact test (for categorical variables). A *P* value below 0.05 was considered statistically significant. Data were analyzed by means of Statistica 6.0 software (StatSoft, Inc., Tulsa, Oklahoma, USA).

Results

In this study we included 30 patients – 13 in the sildenafil group and 17 in the control group. There was no difference in demographic and preoperative data between the sildenafil and the control group (Table 1); only peripheral oxygen saturation tended to be lower in the sildenafil group ($P=0.06$). There was no difference between the intraoperative and postoperative parameters (Table 2) for mortality or operative time. In the control group the total drainage loss (1770 ± 310 vs. 1350 ± 230 ml; $P=0.0003$), the relative drainage loss ($P=0.0045$), and persistence time ($P=0.0004$) were greater. Required chest tube reinsertion after removal of the drains was similar in the two groups (2/4; $P=0.50$). The hemodynamic parameters showed a better condition in the sildenafil group, with a lower mPAP ($P=0.0001$) and a better mPAP/mSBP ratio ($P=0.0043$), whereas there was no difference in peripheral oxygen saturation ($P=0.31$). The sildenafil group had a lower inotropic score ($P=0.0005$), intubation time ($P=0.0004$), timing for chest drainage removal ($P=0.0004$), and ICU stay ($P=0.0001$). No complications related to the use of sildenafil were noted in any of the children studied.

Discussion

Pulmonary circulation plays an important role in mortality and morbidity after right heart bypass surgery, including the Fontan-type procedure and bidirectional cavopulmonary shunt.^{7,8} Severe impairment of the pulmonary circulation only occurs infrequently after right heart bypass surgery, but such impairment causes increased central venous pressure and decreased left-heart preload, leading to severe congestion in the major organs and low cardiac output syndrome, respectively. There are various options for treatment of impaired pulmonary circulation, including intravenous trinitroglycerine (TNG), prostaglandin E1, prostacyclin and inhaled nitric oxide.⁹ Sildenafil has recently been used to treat various types of pulmonary hypertension. Sildenafil is a selective phosphodiesterase-5 (PDE-5) inhibitor, the predominant PDE isoform responsible for hydrolysis of guanosine 3',5'-cyclic monophosphate (cGMP) in vascular smooth muscle cells in the lungs.

Patients who undergo Fontan procedure or bidirectional cavopulmonary shunt may have a pulmonary vascular dysfunction,¹⁰ with blunted release of endothelium-derived nitric oxide. This is consequent to the loss of flow pulsatility in the pulmonary circulation. Pulmonary endothelial dysfunction might lead to increased pulmonary vascular resistance and attenuation of the physiologic lowering of pulmonary vascular resistance induced by nitric oxide release. Administration of the selective pulmonary vasodilator-inhaled nitric oxide to patients with Fontan circulation reduces pulmonary vascular resistance.¹⁰ However, nitric oxide has a high selectivity for the pulmonary circulation, with the potential disadvantage of increasing pulmonary capillary wedge pressure in patients with systemic ventricular dysfunction.¹¹ Further, in a previous study, nitric oxide failed to increase cardiac output (*CO*) in Fontan patients.¹⁰ Sildenafil has been shown to be as effective a pulmonary vasodilator as inhaled nitric oxide in patients with pulmonary arterial hypertension, and in children with CHD.^{1–3,10} Sildenafil was also recently shown to be able to increase exercise

Table 2 Intraoperative and postoperative parameters

	Sildenafil group (<i>n</i> = 13)	Control group (<i>n</i> = 17)	<i>P</i> value
Mortality (in the first 30 days)	0	1	0.58
Total operation time (min)	355 \pm 42	378 \pm 68	0.29
CPB time (min)	67 \pm 13	64 \pm 10	0.48
mPAP (mmHg) (after 72 h)	12.6 \pm 1.1	14.7 \pm 1.4	0.0001
mPAP/mSBP (after 72 h)	0.20 \pm 0.02	0.23 \pm 0.03	0.0043
SpO ₂ (%) (after 72 h)	98.3 \pm 1.5	97.6 \pm 2.1	0.31
Total drainage loss (ml)	1350 \pm 230	1770 \pm 310	0.0003
Relative drainage loss (ml/kg)	68.5 \pm 11.6	83.8 \pm 14.7	0.0045
Chest drainage removal (days)	5.9 \pm 1.1	7.7 \pm 1.3	0.0004
Creatinine (mg/dl) (after 72 h)	0.7 \pm 0.2	0.8 \pm 0.3	0.30
Inotropic score	18.5 \pm 4	27 \pm 7	0.0005
Fluid balance (in first 72 h) (ml)	–190 \pm 70	–210 \pm 90	0.51
Intubation time (h)	15.5 \pm 4	23.3 \pm 6	0.0004
ICU stay (h)	86 \pm 10	109 \pm 16	0.0001

CPB, cardiopulmonary bypass; mPAP, mean pulmonary artery pressure; mSBP, mean systemic blood pressure; SpO₂, peripheral oxygen saturation.

capacity and pulmonary hemodynamics in pulmonary hypertension or acquired heart failure patients.¹² The successful use of pulmonary vasodilators has been reported in postoperative Fontan patients. Yoshimura *et al.*¹³ have reported the significant benefit of nitric oxide to central venous pressure and transpulmonary gradient after Fontan-type operations. To prevent the rebound effects of inhaled nitric oxide, epoprostenol has also been used in combination for postoperative patients.¹⁴ Several cases of successful treatment with sildenafil have been reported in patients with findings of protein-losing enteropathy and plastic bronchitis.^{15–17}

As experience with sildenafil in cardiac surgery is limited to few studies, the optimal dose has not been established yet.

In our study, a low dose (0.35 mg/kg) of oral sildenafil was used after Fontan operation without concomitant pulmonary vasodilators. No complications related to the use of sildenafil were noted in our series, but a randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil has shown that high doses increase adverse events.¹⁸

Many variables after surgery were better in the sildenafil group without complications related to sildenafil therapy. Particularly, hemodynamic parameters showed a better condition with a lower mPAP, a better mPAP/mSBP ratio, and a lower inotropic score, used as an independent predictor of clinical outcome in infants after cardiac surgery.¹⁹ Also the total and relative drainage losses were lower in the sildenafil group with lower persistence time of chest drainage. There were no exclusion criteria, but in this period we did not have patients with PVR more than 2.5 Wood units. Certainly, there will be some high-risk Fontan patients who could benefit from having sildenafil therapy.

To our knowledge, this is the first case series of patients undergoing Fontan operation, who had been treated with sildenafil in the postoperative period and compared with a control group.

Study limitations

The retrospective design of this study on a small number of patients naturally impedes inference of possible causalities. A historical control group is utilized, but alterations and improvements in the surgical procedures and perioperative environment between the two periods can obviously not be ruled out. Accordingly, a large multicenter, randomized controlled trial with established doses is warranted to validate the efficacy of sildenafil in comparison with placebo or other vasodilators drugs.

In summary, this initial experience suggests that oral sildenafil can be an effective agent to approach the Fontan circulation with a positive effect in postoperative management, but further studies, larger and randomized, are necessary to determine the efficacy, safety and optimal dosing in children following cardiac surgery.

References

- 1 Trachte AL, Lobato EB, Urdaneta F, *et al.* Oral sildenafil reduces pulmonary hypertension after cardiac surgery. *Ann Thorac Surg* 2005; **79**:194–197.
- 2 Peiravian F, Amirghofran AA, Borzouee M, *et al.* Oral sildenafil to control pulmonary hypertension after congenital heart surgery. *Asian Cardiovasc Thorac Ann* 2007; **15**:113–117.
- 3 Palma G, Giordano R, Russolillo V, *et al.* Sildenafil therapy for pulmonary hypertension before and after pediatric congenital heart surgery. *Tex Heart Inst J* 2011; **38**:238–242.
- 4 Morchi GS, Ivy DD, Duster MC, *et al.* Sildenafil increases systemic saturation and reduces pulmonary artery pressure in patients with failing Fontan physiology. *Congenit Heart Dis* 2009; **4**:107–111.
- 5 Beghetti M, Aggoun Y, Da Cruz E. Nitric oxide precursors and congenital cardiac surgery: a randomized controlled trial of oral citrulline. Definition of pulmonary hypertension in Fontan circulation? *J Thorac Cardiovasc Surg* 2006; **132**:1501–1502.
- 6 Wernovsky G, Wypij D, Jonas RA, *et al.* Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation* 1995; **2**:2226–2235.
- 7 Gentles TL, Meyer JE Jr, Gauvreau K, *et al.* Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. *J Thorac Cardiovasc Surg* 1997; **114**:376–391.
- 8 Knott-Craig CJ, Danielson GK, Schaff HV, *et al.* The modified Fontan operation: an analysis of risk factors for early postoperative death and takedown in 702 consecutive patients from one institution. *J Thorac Cardiovasc Surg* 1995; **109**:1237–1243.
- 9 Leuchte HH, Schwaiblmair M, Baumgartner RA, *et al.* Hemodynamic response to sildenafil, nitric oxide, and iloprost in primary pulmonary hypertension. *Chest* 2004; **125**:580–586.
- 10 Khambadkone S, Li J, de Leval MR, *et al.* Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. *Circulation* 2003; **107**:3204–3208.
- 11 Loh E, Stamler JS, Hare JM, *et al.* Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. *Circulation* 1994; **90**:2780–2785.
- 12 Giardini A, Balducci A, Specchia S, *et al.* Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J* 2008; **29**:1681–1687.
- 13 Yoshimura N, Yamaguchi M, Oka S, *et al.* Inhaled nitric oxide therapy after Fontan-type operations. *Surg Today* 2005; **35**:31–35.
- 14 Miyaji K, Nagata N, Miyamoto T, Kitahori K. Combined therapy with inhaled nitric oxide and intravenous epoprostenol (prostacyclin) for critical pulmonary perfusion after the Fontan procedure. *J Thorac Cardiovasc Surg* 2003; **125**:437–439.
- 15 Apostolopoulou SC, Papagiannis J, Rammos S. Bosentan induces clinical, exercise and hemodynamic improvement in a pretransplant patient with plastic bronchitis after Fontan operation. *J Heart Lung Transplant* 2005; **24**:1174–1176.
- 16 Haseyama K, Satomi G, Yasukochi S, *et al.* Pulmonary vasodilation therapy with sildenafil citrate in a patient with plastic bronchitis after the Fontan procedure for hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg* 2006; **132**:1232–1233.
- 17 Uzun O, Wong JK, Bhole V, Stumper O. Resolution of protein-losing enteropathy and normalization of mesenteric Doppler flow with sildenafil after Fontan. *Ann Thorac Surg* 2006; **82**:e39–e40.
- 18 Barst RJ, Ivy DD, Gaitan G, *et al.* A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension. *Circulation* 2012; **125**:324–334.
- 19 Gaies MG, Gurney JG, Yen AH, *et al.* Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010; **11**:234–238.