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Original Article

Sildenafil in the management of the failing Fontan circulation

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Abstract *Background:* Sildenafil is increasingly being used in the management of pulmonary arterial hypertension in the newborn. Its role in patients with congenital cardiac disease is less well defined and as yet has only been reported sporadically. *Aim:* Present our experience with sildenafil treatment in patients with a failing Fontan circulation. *Patients and methods:* Retrospective review of 13 symptomatic patients after Fontan palliation who received treatment with sildenafil between January, 2006 and July, 2008. *Results:* Three patients suffered from protein-losing enteropathy, four patients presented with bronchial casts, two had severe cyanosis after fenestrated Fontan procedure, two had prolonged chylous effusions, one had a previous failure of Fontan and take-down, and one patient had arrhythmias and end-stage cardiac failure requiring conversion to an extra-cardiac Fontan. Sildenafil was used in the dosage of 1–2 milligrams per kilogram 3–4 times per day. Protein-losing enteropathy and α-1-antitrypsin levels improved in all three patients on sildenafil treatment. One of these patients had a concomitant catheter creation of a fenestration, as did two patients presenting with bronchial casts and both patients with persistent chylous effusions. All four patients with bronchial casts and two patients with cyanosis improved significantly on sildenafil treatment. Chylous effusions decreased after sildenafil and stent enlargement of a fenestration. There were no significant side effects requiring sildenafil withdrawal over a treatment period ranging from 2 months to 2 years. *Conclusions:* Sildenafil can be used safely and effectively in the treatment of patients with a failing Fontan circulation.

Keywords: Fontan fenestration; protein-losing enteropathy; pulmonary vascular resistance

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FONTAN CIRCULATION PROVIDES VERY GOOD MEDIUM-term palliation for patients with a single ventricle. Nonetheless, the physiology is severely altered from normal including persistent low cardiac output state, high systemic vascular resistance and pulmonary vascular resistance, elevated central venous pressure, systolic and diastolic ventricular dysfunction, and abnormal arterial and venous haemodynamics.[1] A significant number of Fontan patients will develop early or late complications including ventricular dysfunction, arrhythmias, persistent hypoxaemia, protein-losing enteropathy, bronchial casts, prolonged pleural effusions, thromboembolism, and stroke.[2–5] Hosein et al[6] showed in their study that elevated pulmonary artery pressure preoperatively has an adverse influence on Fontan outcome.

The creation of a Fontan circulation causes loss of pulsatile pulmonary blood flow. This results in endothelial dysfunction with a decrease in the sheer stress-mediated release of endothelium-derived nitric oxide and causes an increase in pulmonary vascular resistance.[7] On the basis of growing experience with oral sildenafil in the treatment of persistent pulmonary hypertension of the newborn and pulmonary arterial hypertension in children,[8,9] we postulated that sildenafil would be of benefit in patients with failing Fontan circulation.

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Patients and methods

This study included 13 consecutive patients with severe Fontan complications presenting to either Birmingham Children's Hospital, or to the Department of Paediatric Cardiology, University Hospital Wales, Cardiff, over a period of 30 months from January, 2006 to July, 2008. The mean age at the completion of the Fontan circulation was 4.5 (2.6–10) years. The mean interval between Fontan completion and the onset of complications was 2.5 (0.1–13) years. Sildenafil was given at a dose of 1–2 milligrams per kilogram 3–4 times per day. Treatment duration was between 2 months and 2 years and was weaned off gradually according to clinical response.

Four patients presented with bronchial casts, three patients suffered from protein-losing enteropathy, two had severe cyanosis after fenestrated Fontan, two had prolonged chylous effusions, one had previous failure of Fontan and take-down, and one had arrhythmias and end-stage cardiac failure and required conversion to an extra-cardiac Fontan.

Results

All four patients with bronchial casts improved significantly on sildenafil treatment. Two of these underwent concomitant catheter creation of a fenestration. One patient (no. 1) had previous stenting of a Fontan fenestration for bronchial casts with good effect. He later developed progressive right-ventricular dysfunction and the bronchial casts recurred. Sildenafil treatment was commenced and the casts improved but recurred early after successful cardiac transplantation. Sildenafil therapy was re-initiated with good effect and could be stopped some 3 months after transplantation.

In all three patients with protein-losing enteropathy, the serum albumin levels and the stool α-1-antitrypsin levels improved significantly on sildenafil treatment. Patient no. 5 initially was treated conservatively with a high-protein and medium-chain triglyceride diet, steroids and heparin, but developed significant side effects including osteoporosis. When referred to our unit, she was found to have a restriction to pulmonary venous return and thus underwent atrial septectomy and conversion to a fenestrated Fontan circulation. She was left with marked cyanosis and underwent partial catheter device occlusion of the fenestration. The protein-losing enteropathy recurred and she was commenced on sildenafil treatment with good effect.

Patient no. 6 underwent total catheter device occlusion of a large fenestration 6 months after the completion of an extracardiac, fenestrated Fontan procedure. He had a poor functional result and was diagnosed late with florid protein-losing enteropathy – albumin 19 grams per decilitre and α-1-antitrypsin 17.6 milligrams per gram. He underwent concomitant commencement of sildenafil treatment and transcatheter stent fenestration of his Fontan circulation with good result. Subsequently, he underwent dual-chamber epicardial pacing with complete resolution of protein-losing enteropathy. Patient no. 7 is stable on sildenafil treatment and high-protein diet.

Sildenafil was used in two patients for severe persistent chylous effusions early after Fontan completion in conjunction with stent augmentation of the Fontan fenestration with good result. In two patients with severe cyanosis after fenestrated Fontan procedure, sildenafil was used with an observed rise in resting and exercise saturations and clinical improvement. One went on to undergo partial Fontan fenestration closure and one had surgical resection of a restrictive atrial septum.

Sildenafil was used perioperatively in two patients having creation/conversion of an extracardiac Fontan with good effect Details of all patients are included in Table 1.

There were no significant side effects requiring sildenafil withdrawal over the treatment period. Medium treatment duration was 8 months, with a range of 2–25 months, with 6 of the 13 (46%) patients continuing on sildenafil treatment.

Discussion

The Fontan procedure provides high-grade palliation for patients with functionally univentricular hearts. Many of the immediate and long-term problems after a Fontan procedure, such as prolonged pleural effusions, persistent hypoxaemia, protein-losing enteropathy, and bronchial casts are pathophysiologically not fully understood and remain a challenge for treatment.[1]

Potentially treatable residual anatomic or haemodynamic lesions should be excluded meticulously. Steroids and heparin have been used with varying degrees of success in the management of protein-losing enteropathy and plastic bronchitis.[3–5,10] In addition, various interventions including pacemaker implantation, transcatheter Fontan fenestration, and stent fenestration of the atrial septum have been reported in the management of patients with Fontan complications.[11]

Even though the pathophysiology of protein-losing enteropathy and plastic bronchitis is speculative,[4,5] we based our treatment strategy with sildenafil on the concept that the lack of pulsatile flow within the Fontan circulation contributes to pulmonary endothelial dysfunction and an increase in the overall pulmonary vascular resistance.[7]

Sildenafil is a selective inhibitor of cyclic guanosine–monophosphate-specific phosphodiesterase type 5. It is

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Table 1. Details of patients.

No.	Diagnosis	Age at Fontan	Type of Fontan	Interval	Presenting Symptoms	Concomitant therapy	Sildenafil dose (mg/kg)	Sildenafil duration (weeks) and outcome
1	Hypoplastic left cardiac syndrome	3.3	Lateral tunnel	3.5	Bronchial casts		0.6; 3 times per day	14
2	Tricuspid atresia, pulmonary atresia	4.4	Extracardiac fenestrated Fontan	8.0	Bronchial casts		1.2; 4 times per day	134
3	Double outlet right ventricle, straddling mitral valve	3.3	Lateral tunnel	6.5	Bronchial casts	Stent Fenestration	0.9; 4 times per day	52
4	Tricuspid atresia, severe pulmonary stenosis	5.3	Extracardiac non-fenestrated Fontan		Bronchial casts	Left pulmonary artery stent, stent Fenestration	1.0; 3 times per day	Still on sildenafil
5	Hypoplastic left cardiac syndrome	2.5	Lateral tunnel	4.0	Protein-losing enteropathy	Atrial septectomy, conversion to extracardiac, fenestrated Fontan, protein-losing enteropathy re-occurred partial catheter device occlusion of the fenestration due to cyanosis	1.0; 4 times per day	Transferred care, still on sildenafil (albumin level: pre-sildenafil, <30; post-sildenafil, 39; time to improve, 9 days)
6	Hypoplastic left cardiac syndrome	3.9		8.0	Protein-losing enteropathy	Left pulmonary artery stent, stent fenestration, dual-chamber epicardial pacing	1.0; 3 times per day	143 (albumin level: pre-sildenafil, 22; post-sildenafil, 37 – time to improve, 68 days)
7	Complete atrioventricular septal defect, right atrial isomerism, total anomalous pulmonary venous connection	10	Extracardiac fenetrated Fontan	11	Protein-losing enteropathy			30 (albumin level: pre-sildenafil, 23; post-sildenafil, 47 – time to improve, 120 days)
8	Hypoplastic left cardiac syndrome	7	Extracardiac fenestrated Fontan	0.1	Chylous effusions, high right-ventricular pressure	Stenting of fenestration	1.0; 4 times per day	15; treatment withdrawn
9	Unbalanced complete atrioventricular septal defect (small left ventricle)	3.5	Extracardiac fenestrated Fontan	0.1	Chylous effusions	Stenting of fenestration	1.4; 3 times per day	Still on sildenafil; drains removed 25 days after sildenafil treatment commenced
10	Hypoplastic left cardiac syndrome	5	Extracardiac fenestrated Fontan	5.0	Cyanosis		1.8; 3 times per day	48
11	Hypoplastic left cardiac syndrome	5	Extracardiac fenestrated Fontan	4.1	Cyanosis	Atrial septectomy	0.90; 3 times per day	43
12	Double outlet right ventricle, mitral atresia, coarctation of aorta, total anomalous pulmonary venous drainage	12.5	Extracardiac fenestrated Fontan	12.6	Previous failure, take down of Fontan	Closure of Fontan fenestration, dual-chamber epicardial pacing	1.8; 4 times per day	6
13	Absent right atrioventricular valve	2.1	Classical Fontan	15.1	Arrhythmias, poor haemodynamics, required Fontan conversion		0.5; 3 times per day	Transferred care, still on sildenafil

effective even in the absence of a functional endothelium. Phosphodiesterase 5 inhibitors cause pulmonary vasodilatation by promoting an enhanced and sustained level of cyclic guanosine monophosphate. Sildenafil was successfully used in the treatment of a case of plastic bronchitis after the Fontan procedure.[10] In addition, sildenafil was shown to have a direct effect on mesenteric vascular resistance, leading to a normalisation of the mesenteric Doppler flow and resolution of protein-losing enteropathy in a case of a failing Fontan circulation.[12] There are several animal and human studies with specific phosphodiesterase type 5 inhibitors and they have an effect on mesenteric and portal circulation. Sildenafil and vardenafil have been shown to reduce portal venous pressure and increase mesenteric blood flow.[13,14]

Sildenafil has a list of side effects occurring in up to 5% of patients. These unwanted effects include headache, dizziness flushing, dyspepsia, penile erection, nasal congestion, abnormal vision, diarrhoea, and hypersensitivity reaction including rash and priapism. Sildenafil drug level increases significantly if used concomitantly with erythromycin and cimetidine. None of our patients had significant side effects.

There were 13 patients with significant early or late Fontan problems who were treated with sildenafil in our study. Although the mechanism of protein-losing enteropathy or bronchial casts is not fully understood, we argued that an elevated systemic venous pressure, together with increased pulmonary and mesenteric vascular resistance, may be key elements in the pathophysiology, and thus the use of an oral pulmonary vasodilator should be of benefit. As a number of the patients in this study were very unwell at the time of presentation, 5 of 13 patients underwent concomitant catheter interventions in the form of stent enlargement or the creation of a fenestration combined with stenting of a narrow left pulmonary artery in two patients. Thus, strictly speaking, the individual contribution of either sildenafil treatment or catheter intervention to the clinical improvement in these cases cannot be fully ascertained. In addition, serial measurements of the semi-quantitative data, such as a 6-minute walk distance, cardiac output, or measurements of systemic venous pressures or pulmonary vascular resistance could not be obtained. A recent study by Giardini et al[15] showed that oral administration of a single dose of sildenafil in Fontan patients improved exercise capacity and haemodynamic response to exercise.

Conclusion

Sildenafil can be used safely and effectively in patients with failing Fontan circulation. It should be considered as an adjunct to the treatment of patients presenting with severe Fontan complications, which may be related to increased pulmonary vascular resistance. Prospective randomised controlled trials of sildenafil treatment in patients with Fontan circulation should be undertaken.

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