Cardiology in the Young (2015), **25**, 1136–1140
doi:10.1017/S1047951114001772

Original Article

Pulmonary vasodilator therapy and early postoperative outcome after modified Fontan operation

Alberto Mendoza,[1] Leticia Albert,[1] Sylvia Belda,[2] Lidia Casanueva,[2] Dolores Herrera,[1] Miguel A. Granados,[1] José M. Velasco,[1] Enrique García,[1] Juan M. Aguilar,[1] Juan V. Comas[1]

[1]*Pediatric Heart Institute;* [2]*Pediatric Intensive Care Unit, Hospital Universitario 12 de Octubre, Madrid, Spain*

Abstract Although mortality is low after the modified Fontan procedure, there is a significant percentage of patients with prolonged postoperative recovery. The objective of this study is to evaluate the usefulness of postoperative administration of oral sildenafil and inhaled nitric oxide on early postoperative outcome.

A prospective interventional and comparison study with a historical cohort was conducted. Between January, 2010 and March, 2013, 16 patients received oral sildenafil during immediate modified Fontan postoperative period. Inhaled nitric oxide was also administered if the patient was kept intubated 12 hours after surgery. Early postoperative outcome was compared with a historical cohort of 32 patients on whom the modified Fontan procedure was performed between March, 2000 and December, 2009.

Postoperative administration of sildenafil and nitric oxide had no influence on early postoperative outcome after the modified Fontan procedure in terms of duration of pleural effusions, mechanical ventilation time, length of stay in the ICU, and length of hospital stay.

Keywords: Modified Fontan operation; pulmonary vasodilators; sildenafil; inhaled nitric oxide; CHD

Received: 27 May 2014; Accepted: 24 August 2014; First published online: 16 September 2014

Since its initial description in 1971, the Fontan procedure[1] has undergone significant modifications in patient preparation, surgical technique, and postoperative management, which have reduced both mortality and postoperative hospital stay.[2–4]

Nevertheless, after the modified Fontan procedure, there is still a significant percentage of patients with a prolonged postoperative length of stay.[2,5] One of the risk factors contributing to morbidity after surgery is the elevation of pulmonary vascular resistance.[5,6,7] In the early postoperative period, pulmonary vascular resistance is more labile owing to pulmonary endothelial dysfunction after cardiopulmonary bypass. In this condition, even minor pulmonary vascular resistance elevations may lead to serious reduction in pulmonary flow and a low cardiac output syndrome. In this sense, maintenance of a low pulmonary vascular resistance becomes a priority during the immediate postoperative period.

In recent years, growing attention has been paid to the usefulness of pulmonary vasodilators in patients with Fontan circulation.[8–10] Nevertheless, to date, there are no studies that have assessed the usefulness of oral sildenafil during the immediate postoperative period after the modified Fontan procedure.

Materials and methods

Patients

Between January, 2010 and March, 2013, 16 patients with univentricular physiology, who had previously undergone a bidirectional Glenn operation, underwent the modified Fontan procedure at our centre.

Correspondence to: A. Mendoza, Instituto Pediátrico del Corazón, Hospital Universitario 12 de Octubre, Avenida de Córdoba s/nº, 28041, Madrid, Spain. Tel: +34913908508/+34913908347; Fax: +3491 390 87 72; E-mail: alberto.mendoza@salud.madrid.org

Demographic, anatomic, haemodynamic, procedural, and postoperative variables were recorded from the medical records (Table 1).

All patients were catheterised in the preceding 6-month period before the Fontan procedure. We collected data on the surgical techniques used, such as extracardiac or lateral tunnel Fontan, surgery with cardiopulmonary bypass, cross-clamping and circulatory arrest, surgical times, and associated procedures. Postoperative Fontan and left atrial pressure were monitored and transpulmonary gradient was calculated. We collected data on the duration of postoperative pleural effusions, mechanical ventilation time, length of stay in the paediatric ICU, and length of hospital stay. We also recorded immediate postoperative complications and mortality.

Study design

The 16 patients of the study – postoperative pulmonary vasodilator group – received oral sildenafil with an average dose of 4.6 ± 1.6 mg/kg/day in three divided doses. Treatment began during the first 24 hours following operation and continued at least until hospital discharge. Treatment cessation was decided by the responsible cardiologist, but always on the base of a stable clinic situation after Fontan surgery and never before the closure of the fenestration, when it had been made. Average treatment duration after surgery was 10 months [interquartile range 7–22]. If the patient remained intubated 12 hours after surgery, he/she also received inhaled nitric oxide until extubation. Of the patients, six received a maximum inhaled nitric oxide dose of 20 ppm during 36 hours

Table 1. Clinical, haemodynamic, preoperative, and postoperative characteristics of the study cohorts.

Variable	Control (n = 32)	Vasodilator group (n = 16)	p
Demographics			
Gender (male/female)	15/17	9/7	0.76
Age at Fontan (years)	5.4 ± 1.7	5.7 ± 2.7	0.56
Weight at Fontan (kg)	17.5 ± 4.2	18.5 ± 6.5	0.66
Preoperative clinical data			
Heterotaxy	4 (12%)	0 (0%)	0.28
HLHS	7 (22%)	4 (25%)	0.64
Systemic right ventricle	12 (37%)	4 (25%)	0.38
Norwood surgery	8 (25%)	7 (43%)	0.18
Moderate–severe AV regurgitation	5 (16%)	2 (12%)	0.55
Moderate–severe ventricular dysfunction	2 (6%)	0 (0%)	0.43
Preoperative haemodynamics			
mPAP (mmHg)	12.1 ± 2.7	12.7 ± 1.8	0.44
TPG (mmHg)	3.1 ± 1.7	3.8 ± 1.3	0.16
PVR (WU·m^2)	0.9 ± 0.4	1.1 ± 0.4	0.18
EDVP (mmHg)	10.8 ± 2.9	10 ± 1.9	0.29
Nakata index (mm^2/m^2)	252 ± 101	227 ± 72	0.38
Surgical data			
Extracardiac Fontan/lateral tunnel Fontan	25/7	16/0	0.07
Fenestration	12 (38%)	9 (56%)	0.21
Surgery without CPB	3 (10%)	7 (44%)	**0.01**
CPB time (minutes)	143 ± 51	146 ± 66	0.88
Cross clamping	11 (35%)	3 (19%)	0.32
Cross clamping time (minutes)	78 ± 37	67 ± 50	0.67
Postoperatory evolution			
Hospital mortality	1 (3%)	0 (0%)	1
Fontan pressure (mmHg)	14.1 ± 3.3	14.7 ± 2.4	0.55
TPG (mmHg)	5.3 ± 2.3	6.1 ± 2	0.39
Mechanical ventilation time (hours)	18 [7–36]	10 [8–23]	0.43
Length of stay in PICU (days)	5 [4–10]	6 [5–8]	0.72
Duration of pleural effusions (days)	18 ± 11.9	14 ± 6.7	0.22
Length of hospital stay (days)	24 [15–29]	21 [16–29]	0.80
Infection	19 (59%)	10 (62%)	1
Arrhythmia	8 (25%)	1 (6%)	0.23
Neurologic complication	7 (22%)	2 (12%)	0.69
Reoperation	3 (10%)	0 (0%)	0.54

AV = atrioventricular, CPB = cardiopulmonary bypass; EDVP = end diastolic ventricular pressure; HLHS = hypoplastic left heart syndrome; mPAP = mean pulmonary artery pressure; PICU = paediatric ICU; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient; WU = Wood units

Data are expressed as n (%), mean ± standard deviation or median [interquartile range]

https://doi.org/10.1017/S1047951114001772 Published online by Cambridge University Press

[interquartile range 8.5–78]. There were no adverse effects of the medication.

This group was compared with our previously published[11] historical cohort of 32 patients operated between March, 2000 and December, 2009 (control group).

The local ethics committee approved the study protocol. Informed consent was obtained from the parents of all patients.

Statistical analysis

Continuous variables were expressed as means (standard deviations) or medians [interquartile range]. Categorical variables are shown as frequencies and percentages. Student's t-test was used for between-group comparisons with normally distributed continuous variables. The Mann–Whitney test was used for variables showing a non-normal distribution. Linear regression was used to analyse correlations between continuous variables. Comparisons between categorical variables were made using the χ^2-test or Fisher's exact test. Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, Illinois, United States).

Results

There were no significant differences in the clinical characteristics or catheterisation data between the postoperative pulmonary vasodilator and control groups. Regarding the surgical variables, in the postoperative pulmonary vasodilator group, there were no patients with lateral tunnel Fontan, and the percentage of patients who underwent surgery without cardiopulmonary bypass was significantly greater than the control group. Regarding postoperative variables, there were no significant differences between the prophylactic vasodilator and control groups (Table 1). No patient in the postoperative pulmonary vasodilator group died.

Discussion

Different studies have shown that the main determinants of cardiac output after the Fontan procedure are: the cavopulmonary connection itself,[12] the size of the pulmonary arteries,[13] and pulmonary vascular resistance.[14]

With regard to the cavopulmonary connection, it seems connection geometry,[15] conduit size,[16] or connection type[17] – lateral tunnel versus extracardiac conduit – not only influence haemodynamics but also clinical evolution after the Fontan procedure.

Other studies have found that the area of the pulmonary arteries correlates with cardiac output.[13] Moreover, theoretical models have been calculated for the minimum area of pulmonary arteries compatible with a low-pressure Fontan.[18]

Nevertheless, most authors support the fact that pulmonary vascular resistance is the major determining factor of cardiac output and clinical evolution in patients with Fontan physiology.[14] Supporting this theory, on the one hand, is the fact that in most series preoperative and postoperative pressures and pulmonary vascular resistance accounted for the main morbidity and mortality risk factors.[5–7,11] In a recent study,[3] the cut-off point that predicted bad postoperative evolution was a mean pulmonary artery pressure of $\geqslant$15 mmHg during catheterisation before surgery. On the other hand, the anatomopathological study on lungs in patients with failed Fontan shows a high rate of alterations in pulmonary vasculature[19] characterised by medial hypertrophy in the preacinar arterioles[20] and muscularisation of the intraacinar arteries.[21]

During early postoperative period, labile pulmonary vascular resistance may predispose to increase in pulmonary pressures leading to low output and Fontan failure, despite a technically successful procedure. This elevation of pulmonary vascular resistance is due to endothelial dysfunction after the cardiopulmonary bypass mediated by a reduction in the endogenous nitric oxide production of the pulmonary endothelial cells and subsequent local reduction of its vasodilator effect,[22,23] along with an increase in endothelin levels acting as a pulmonary vasoconstrictor, the levels of which have been correlated with pulmonary vascular resistance in patients during postoperative Fontan.[24]

Evidence that pulmonary vasculature plays a critical role in univentricular circulation functioning has fostered growing interest in the use of pulmonary vasodilators in Fontan patients.[8]

Both inhaled nitric oxide and sildenafil are powerful pulmonary vasodilators that have demonstrated their effectiveness in treating pulmonary hypertension in biventricular heart patients.[25,26]

Different studies have proven the usefulness of inhaled nitric oxide during immediate postoperative period after the Fontan procedure in patients with reduced pulmonary perfusion because of high pulmonary vascular resistance. In these studies, inhaled nitric oxide administration reduced the pressure in Fontan, the transpulmonary gradient, and improved oxygenation.[27,28] However, it seems that the response is not identical in all patients and is greater in those with oxygen saturation <85%, pulmonary vascular resistance >2 UW·m^2, Fontan pressure $\geqslant$15 mmHg, and transpulmonary gradient $\geqslant$8 mmHg.[28–30] One of the problems associated with the use of inhaled nitric oxide is the rebound effect of pulmonary pressures after suspension. Combined

https://doi.org/10.1017/S1047951114001772 Published online by Cambridge University Press

administration with a phosphodiesterase inhibitor such as milrinone not only blocks this rebound but also boosts the pulmonary vasodilator effect of both drugs in postoperative Fontan.[31]

Sildenafil has also demonstrated its effectiveness in reducing Fontan postoperative pressure in patients with O2 saturations ⩽85%, Fontan pressure ⩾16 mmHg, or prolonged pleural effusion ⩾2 weeks,[32] as well as in patients with failed Fontan.[33] Isolated cases have been published where sildenafil improved the evolution of serious Fontan complications such as plastic bronchitis[34] or protein-losing enteropathy.[35] Furthermore, different studies have demonstrated that sildenafil improves exercise capacity and cardiac output in patients with Fontan circulation.[36–38]

Our study is the first to assess the usefulness of pulmonary vasodilators administered to non-selected patients after the Fontan procedure. A similar study[9] administered inhaled nitric oxide from the end of the cardiopulmonary bypass until extubation, followed by oral pulmonary vasodilators when digestive tolerance began, with good postoperative results. However, in that study, there was no control group. Beraprost was administered to the majority of patients and sildenafil to only three patients.

The absence of pulmonary vasodilator effects on the postoperative evolution of our Fontan patients may be due to several factors. On the one hand, given the short intubation period, only six patients received nitric oxide. On the other hand, sildenafil administration commenced in the initial hours, in most cases via nasogastric tube. It is highly likely that drug absorption was erratic during the first few days owing to paralytic ileus secondary to the surgery and the low oral intake during the first few postoperative days. Intravenous sildenafil could have been an alternative treatment, but it was not available for us at the beginning of the study.

Fontan surgery was performed at a relatively old age – five and a half years –in our series, what possibly enhanced the appearance of collateral circulation. Other studies[39] have related this increased collateral circulation to higher pressures in the Fontan surgery and longer duration of pleural effusions, necessitating drainages for a longer time period, what could explain the higher incidence of infections. This circumstance could have acted as a confounding factor.

As shown by some studies, there is also the possibility that pulmonary vasodilators are only useful in patients with critically reduced pulmonary perfusion after the Fontan procedure.[28–30]

Study limitations

The main limitations of the study are: the small sample size and the fact that the control group is a historical cohort not contemporary with the study group. Nevertheless, both samples are very similar in most of the variables analysed. Similarly, preoperative and postoperative treatment of these patients did not suffer significant variations between both periods.

Conclusion

The systematic administration of pulmonary vasodilators after the Fontan procedure does not improve early postoperative evolution in these patients.

Acknowledgements

None.

Financial Support

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflict of interest

None.

Ethical Standards

The study was conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (WMA, 2008) and has been approved by the local ethics committee.

References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971; 26: 240–248.
2. Hirsch JC, Goldberg C, Bove EL, et al. Fontan operation in the current era. A 15-year single institution experience. Ann Surg 2008; 248: 402–410.
3. Rogers LS, Glatz AC, Ravishankar C, et al. 18 years of the Fontan operation at a single institution. Results from 771 consecutive patients. J Am Coll Cardiol 2012; 60: 1018–1025.
4. Khairy P, Fernandes SM, Mayer JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008; 117: 85–92.
5. Salvin JW, Scheurer MA, Laussen PC, et al. Factors associated with prolonged recovery after the Fontan operation. Circulation 2008; 118 (Suppl 1): S171–S176.
6. Knott-Craig CJ, Danielson GK, Schaff HV, Puga FJ, Weaver AL, Driscoll DD. The modified Fontan operation. An analysis of risk factors for early postoperative death or takedown in 702 consecutive patients from one institution. J Thorac Cardiovasc Surg 1995; 109: 1237–1243.
7. Gentles TL, Mayer JE, 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. Beghetti M. Fontan and the pulmonary circulation: a potential role for new pulmonary hypertension therapies. Heart 2010; 96: 911–916.
9. Harada Y, Uchita S, Sakamoto T, et al. Do we need fenestration when performing two-staged total cavopulmonary connection

using an extracardiac conduit? Interact Cardiovasc Thorac Surg 2009; 9: 50–55.
10. Beghetti M, Tissot C. Hipertensión pulmonar en los cortocircuitos congénitos. Rev Esp Cardiol 2010; 63: 1179–1193.
11. Mendoza A, Albert L, Ruiz E, et al. Operación de Fontan. Estudio de los factores hemodinámicos asociados a la evolución postoperatoria. Rev Esp Cardiol 2012; 65: 356–362.
12. Sundareswaran KS, Pekkan K, Dasi LP, et al. The total cavopulmonary connection resistance: a significant impact on single ventricle hemodynamics at rest and exercise. Am J Physiol Heart Circ Physiol 2008; 295: H2427–H2435.
13. Dasi LP, KrishnankuttyRema R, Kitajima HD, et al. Fontan hemodynamics: importance of pulmonary artery diameter. J Thorac Cardiovasc Surg 2009; 137: 560–564.
14. Gewillig M, Brown SC, Eyskens B, et al. The Fontan circulation: who controls cardiac output? Interact CardioVasc Thorac Surg 2010; 10: 428–433.
15. Bove EL, de Leval MR, Migliavacca F, Guadagni G, Dubini G. Computational fluid dynamics in the evaluation of hemodynamic performance of cavopulmonary connections after the Norwood procedure for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2003; 126: 1040–1047.
16. Itatani K, Miyaji K, Tomoyasu T, et al. Optimal conduit size of the extracardiac Fontan operation based on energy loss and flow stagnation. Ann Thorac Surg 2009; 88: 565–573.
17. Stewart RD, Pasquali SK, Jacobs JP, et al. Contemporary Fontan operation: association between early outcome and type of cavopulmonary connection. Ann Thorac Surg 2012; 93: 1254–1261.
18. Itatani K, Miyaji K, Nakahata Y, Ohara K, Takamoto S, Ishii M. The lower limit of the pulmonary artery index for the extracardiac Fontan circulation. J Thorac Cardiovasc Surg 2011; 142: 127–135.
19. Mitchell MB, Campbell DN, Ivy D, et al. Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. J Thorac Cardiovasc Surg 2004; 128: 693–702.
20. Yamaki S, Ajiki H, Haneda K, Takanashi Y, Ban T, Takahashi T. Pulmonary arterial changes in patients dying after a modified Fontan procedure following pulmonary artery banding. Heart Vessels 1994; 9: 263–268.
21. Lévy M, Danel C, Tamisier D, Vouhé P, Leca F. Histomorphometric analysis of pulmonary vessels in single ventricle for better selection of patients for the Fontan operation. J Thorac Cardiovasc Surg 2002; 123: 263–270.
22. Törnberg DC, Angdin M, Settergen G, Liska J, Lundberg JO, Weitzberg E. Exhaled nitric oxide before and after cardiac surgery with cardiopulmonary bypass-response to acetylcholine and nitroglycerin. Br J Anaesth 2005; 94: 174–180.
23. Lévy M, Danel C, Laval AM, Leca F, Vouhé P, Israël-Biet D. Nitric oxide synthase expression by pulmonary arteries: a predictive marker of Fontan procedure outcome? J Thorac Cardiovasc Surg 2003; 125: 1083–1090.
24. Hiramatsu T, Imai Y, Takanashi Y, et al. Time course of endothelin-1 and adrenomedullin after the Fontan procedure. Ann Thorac Surg 1999; 68: 169–172.
25. Journois D, Baufreton C, Mauriat P, Pouard P, Vouhé P, Safran D. Effects of inhaled nitric oxide administration on early postoperative mortality in patients operated for correction of atrioventricular canal defects. Chest 2005; 128: 3537–3544.
26. Barst RJ, Ivy D, 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.
27. Gamillscheg A, Zobel G, Urlesberger B, et al. Inhaled nitric oxide in patients with critical pulmonary perfusion after Fontan-type procedures and bidirectional Glenn anastomosis. J Thorac Cardiovasc Surg. 1997; 113: 435–442.
28. Goldman AP, Delius R, Deanfield JE, et al. Pharmacological control of pulmonary blood flow with inhaled nitric oxide after the fenestrated Fontan operation. Circulation 1996; 94 (Suppl II): II44–II48.
29. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. Circulation 2003; 107: 3204–3208.
30. Yoshimura N, Yamaguchi M, Oka S, et al. Inhaled nitric oxide therapy after Fontan-type operations. Surg Today 2005; 35: 31–35.
31. Cai J, Su J, Shi Z, et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. Ann Thorac Surg 2008; 86: 882–888.
32. Uhm JY, Jhang WK, Park JJ, Seo DM, Yun SC, Yung TJ. Postoperative use of oral sildenafil in pediatric patients with congenital heart disease. Pediatr Cardiol 2010; 31: 515–520.
33. Morchi GS, Ivy DD, Duster MC, Claussen L, Chan KC, Kay J. Sildenafil increases systemic saturation and reduces pulmonary artery pressure in patients with failing Fontan physiology. Congenit Heart Dis 2009; 4: 107–111.
34. Haseyama K, Satomi G, Yasukochi S, Matsui H, Harada Y, Uchita Y. 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.
35. 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.
36. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation. A randomized, double-blind, placebo-controlled, crossover trial. Circulation 2011; 123: 1185–1193.
37. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J 2008; 29: 1681–1687.
38. Jackson KW, Butts RJ, Svenson AJ, McQuinn TC, Atz AM. Response to a single dose of sildenafil in single-ventricle patients: an echocardiographic evaluation. Pediatr Cardiol 2013; 34: 1739–1742.
39. Glatz AC, Rome JJ, Small AJ, et al. Systemic-to-pulmonary collateral flow, as measured by cardiac magnetic resonance imaging, is associated with acute post-Fontan clinical outcomes. Circ Cardiovasc Imaging 2012; 5: 218–225.