Bosentan induces clinical and hemodynamic improvement in candidates for right-sided heart bypass surgery

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Objective: To investigate the efficacy of bosentan in patients with single-ventricle physiology who were unable to undergo right-sided heart bypass surgery because of high pulmonary vascular resistance and pulmonary artery pressure.

Methods: Eight patients with single-ventricle physiology (2 male and 6 female; aged 7 months to 5 years, median 1 year) were enrolled. Prior surgical interventions included pulmonary artery banding in 4 patients, Blalock–Taussig shunt operation in 2 patients, and bidirectional Glenn operation in 5 patients. Right-sided heart bypass surgery was contraindicated for all patients because of high pulmonary vascular resistance and pulmonary artery pressure.

Results: Bosentan therapy successfully reduced pulmonary artery pressure and pulmonary vascular resistance in all patients. Mean pulmonary artery pressure at baseline and after bosentan therapy was 21.1 ± 7.2 mm Hg and 11.9 ± 4.1 mm Hg, respectively ($P < .01$). Mean pulmonary vascular resistance index at baseline and after bosentan therapy was 5.7 ± 3.3 U/m² and 1.3 ± 0.4 U/m², respectively ($P < .01$). Mean pulmonary vascular resistance/systemic vascular resistance at baseline and after bosentan therapy was 0.25 ± 0.11 and 0.07 ± 0.03 , respectively ($P < .01$). All patients had improved clinical symptoms and underwent successful Fontan operations.

Conclusion: Bosentan induces mid-term clinical and hemodynamic improvement in patients with single-ventricle physiology and elevated pulmonary vascular resistance and pulmonary artery pressure. Bosentan therapy may increase the surgical options and improve outcomes in candidates for right-sided heart bypass surgery. (J Thorac Cardiovasc Surg 2010;140:346-51)

In recent years, new treatment strategies have largely improved the clinical status and life expectancy of patients with pulmonary artery hypertension (PAH).¹ Bosentan, an oral dual endothelin (A and B) receptor antagonist, has been shown to be effective in patients with idiopathic PAH and PAH related to connective tissue disease, improving long-term quality of life.²⁻⁴ During the past few years, small open-label studies have suggested that bosentan is safe and well tolerated in adults with congenital heart disease (CHD) and that it improves functional status and exercise capacity.^{5,6} These pilot studies triggered the first large randomized controlled trial of bosentan in patients with Eisenmenger syndrome, showing a beneficial short-term effect of bosentan on exercise capacity and hemodynamics without compromising systemic oxygen saturation.⁷

Nonetheless, there are few reports so far on the effect of bosentan on elevated pulmonary artery pressure (PAP) and

pulmonary vascular resistance (PVR) in patients with single-ventricle (SV) physiology. Apostolopoulou and colleagues⁸ reported that bosentan induced clinical, exercise, and hemodynamic improvement in a 14-year-old patient with failing Fontan circulation, high PAP, and plastic bronchitis.⁸ Votava-Smith and colleagues⁹ used bosentan to treat PVR in a 10-year-old patient with SV physiology and a bidirectional Glenn shunt.

Thus, we hypothesized that endothelin may play an important role in maintaining vasoconstriction in SV physiology before and after right-sided heart bypass surgery, and that the endothelin receptor antagonist bosentan may induce hemodynamic improvement in patients with SV physiology with decreased PVR and PAP, which would increase the surgical options. This study examined the efficacy of bosentan in patients with SV physiology who were unable to undergo right-sided heart bypass surgery because of high PVR and PAP.

MATERIALS AND METHODS

Patients

A total of 28 patients with SV physiology underwent cardiac catheterization to evaluate the indication for Fontan operation at the University Hospital of Toyama University between January 2006 and April 2009. Among them, 8 patients were unable to undergo right-sided heart bypass surgery because of high PVR (≥ 3 U/m²) and mean PAP (≥ 18 mm Hg). The remaining 20 patients, who did not have high PVR (< 3 U/m²) and mean PAP (< 18 mm Hg), underwent Fontan operation successfully and were designated the non-PAH group.

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Abbreviations and Acronyms

CHD	= congenital heart disease
NYUPHFI	= New York University Pediatric Heart Failure Index
PAH	= pulmonary artery hypertension
PAP	= pulmonary artery pressure
PVR	= pulmonary vascular resistance
SV	= single ventricle

The degree of heart failure was quantified using the New York University Pediatric Heart Failure Index (NYUPHFI).¹⁰ This score is derived by the linear combination of scores based on symptoms, physical signs, and medical regimen (Table 1). Healthy children without heart failure are expected to score low (<2 points).¹⁰ All enrolled patients had PAH related to CHD with or without prior surgical repair and fixed elevated PVR that precluded further surgical intervention.

Care was taken to exclude other causes of pulmonary hypertension, such as pulmonary arterial hypoplasia, hypoventilation, and lung or liver disease. Patients had no treatment regimen changes within the last month before enrollment and during the study period, aside from the addition of bosentan treatment. No patients were taking epoprostenol, glibenclamide, or cyclosporine, to avoid drug interactions, or calcium channel blockers, because they were unresponsive to vasodilators. All patients were clinically evaluated once every month by electrocardiography, echocardiography, oxygen saturation measurement, and NYUPHFI score assessment. Liver enzyme levels were measured every 2 months in patients treated with bosentan.

The research ethics committee of the University Hospital of Toyama approved the study. Written informed consent was obtained from parents after the purpose and procedures of the study were fully explained.

Study Design

Patients started a twice daily oral bosentan regimen of 0.5 to 1 mg/kg per dose. The dose of bosentan was increased 0.5 to 1 mg/kg every 4 weeks until reaching 3 mg/kg per dose.

All patients were evaluated before initiation and after bosentan treatment regarding history and subjected to clinical examination to define NYUPHFI, an unstructured interview including questions about perceived well-being and exercise ability, and evaluations of maximal and submaximal exercise capacity. Complete hemodynamic studies were simultaneously performed before and after bosentan treatment. Drug safety was evaluated bimonthly by monitoring adverse events, such as flushing and nasal congestion; laboratory tests, such as liver function tests and hemoglobin concentration; electrocardiogram; vital signs; pulse oximetry recordings; and discontinuations.

Cardiac catheterization was performed just before starting bosentan and after bosentan therapy to select surgical options; this was performed under local anesthesia with additional intravenous sodium thiopental. Similarly, cardiac catheterization was performed in the non-PAH group to evaluate the indication of the Fontan operation. Blood gas analysis showed normal partial carbon dioxide acid base status during cardiac catheterization. Pulmonary arterial, right atrial, and pulmonary capillary wedge pressures and systemic pressures were recorded. Systemic and pulmonary arterial and venous saturations were obtained to calculate cardiac outputs with the Fick principle and table-derived oxygen consumption values.¹¹ Oxygen saturations obtained from pulmonary veins, when possible, or several pulmonary capillary wedge positions were used to calculate pulmonary venous oxygen content. For great artery level shunts, oxygen saturations from both distal pulmonary arteries were used to calculate pulmonary arterial oxygen

TABLE 1. New York University Pediatric Heart Failure Index Heart failure severity determined from signs and symptoms, medical regimen, and ventricular physiology

Score	
Signs and symptoms	
+2	Abnormal ventricular function by echocardiogram or gallop
+2	Dependent edema, pleural effusion, or ascites
+2	Failure to thrive or cachexia
+1	Marked cardiomegaly by x-ray or physical examination
+1	Reported physical activity intolerance or prolonged feeding time
+2	Poor perfusion by physical examination
+1	Pulmonary edema by x-ray or auscultation
+2	Resting sinus tachycardia
+2	Retractions
+1	Hepatomegaly
+2	<4 cm below costal margin
+1	>4 cm below costal margin
+2	Observed tachypnea or dyspnea
	Mild to moderate
	Moderate to severe
Medications	
+1	Digoxin
+1	Diuretics
+2	Low to moderate dose
+1	High-dose or > 1 diuretic
+1	ACE-I, other vasodilators, or ARB
+2	β -blockers
+2	Anticoagulants not related to prosthetic valves
	Antiarrhythmic agents or implantable cardiac defibrillator
Physiology	
+2	Single ventricle

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. Adding scores attributed to each individual criterion derives a total score. Scores can range from 0 (no heart failure) to 30 (severe heart failure). Adapted from Connolly D, Rutkowski M, Auslander M, Artman M. The New York University Pediatric Heart Failure Index: a new method of quantifying chronic heart failure severity in children. *J Pediatr*. 2001;138:644-8.

content. Calculation of systemic flow was adequate because oxygen saturations were equal throughout the systemic circuit in all patients. The transpulmonary pressure gradient was defined as the difference between mean PAP and mean pulmonary capillary wedge or left atrial pressure. Pulmonary and systemic vascular resistance indices were calculated with the standard formula.¹² Baseline catheterization studies included hyperoxia or vasodilator challenge to define fixed elevated PVR. Brain natriuretic peptide was quantified at the time of cardiac catheterization. All patients underwent lung perfusion scintigraphy to assess the right-to-left shunt before bosentan therapy.¹³ We combined these data and analyzed pulmonary hemodynamics.

Statistical Analysis

All results were expressed as mean $\pm$ standard deviation. Paired *t* test was used to test for significance of the same parameter within the same group. If data did not follow a normal distribution, the paired *t* test was replaced by a Wilcoxon signed-rank test. When the data followed a normal distribution determined by Shapiro-Wilks test, comparisons between 2 groups were performed using an unpaired Student *t* test or a Welch's test depending on equal or unequal variance. If the data did not follow a normal distribution, then a Mann-Whitney *U* test was used. All *P* values were 2-tailed.

TABLE 2. Baseline clinical and functional characteristics of patients

Patient	Diagnosis	Age	Gender	Pulse oximetry (%)	Symptoms	Medications	NYUPHFI
1	Asplenia, SV, DORV, CoA, TAPVR	9 mo	F	84	Cyanosis	Diuretics, warfarin, aspirin, beraprost	9
2	Asplenia, SV, MA, DORV, TAPVR	8 mo	F	71	DOE, cyanosis	Diuretics, aspirin, beraprost	8
3	Asplenia, SV, DORV, PS, TAPVR	1 y	F	81	DOE, cyanosis	Diuretics, warfarin, aspirin, beraprost, ACE-I, sildenafil	12
4	Asplenia, SV, CAVC, DORV, PS, TAPVR	7 mo	M	80	Cyanosis	Diuretics, warfarin, beraprost, aspirin, ACE-I	9
5	HLHS	10 mo	F	74	Cyanosis	Diuretics, warfarin, aspirin, beraprost, digoxin, ACE-I, β -blocker	11
6	HLHS	2 y	M	75	Cyanosis	Diuretics, warfarin, aspirin, beraprost, digoxin	11
7	HLHS	5 y	F	86	DOE, cyanosis	Diuretics, warfarin, aspirin, beraprost, β -blocker, pimobendan	15
8	SV, DORV, d-MGA	1 y	F	72	Cyanosis	Diuretics, warfarin, aspirin, beraprost, ACE-I, ARB	9

NYUPHFI, New York University Pediatric Heart Failure Index; SV, single ventricle; DORV, double outlet right ventricle; CoA, coarctation of aorta; TAPVR, total anomalous of pulmonary venous return; MA, mitral atresia; PS, pulmonary stenosis; CAVC, complete atrioventricular canal; HLHS, hypoplastic left heart syndrome; d-MGA, d-malposition of the great arteries; DOE, dyspnea on exertion; ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker.

RESULTS

Patient Clinical Characteristics

All 8 patients started bosentan therapy between January 2006 and April 2009, with follow-up through September 2009. Tables 2 and 3 shows the clinical characteristics of the 8 patients with PAH related to CHD, including descriptions of the procedures/surgeries performed. All patients had PAH associated with relative overcirculation to hypoplastic pulmonary vasculature. The 8 patients had higher mean PAP ($P < .01$), higher PVR ($P < .01$), and smaller pulmonary artery index ($P < .01$) compared with the non-PAH group (Table 4). All patients were significantly symptomatic (NYUPHFI score 12.5 ± 2.3) and cyanotic with pulse oximetry (mean $77.9\% \pm 5.6\%$). All patients had taken beraprost before bosentan therapy (median 5.5 months, 1–65 months), but clinical and hemodynamic improvement was not observed because of relative overcirculation to a diminished pulmonary vasculature.

Treatment Effect

Clinical and hemodynamic evaluation was performed at baseline and after 5 to 17 months (mean 8 months). Results at baseline and after bosentan therapy were as follows: mean main PAP: 21.1 ± 7.2 mm Hg and 11.9 ± 4.1 mm Hg, respectively ($P = .0014$); PVR: 5.7 ± 3.3 U/m² and 1.3 ± 0.4 U/m², respectively ($P = .0035$); PVR/systemic vascular resistance: 0.25 ± 0.11 and 0.07 ± 0.03 , respectively ($P = .0009$) (Table 4). However, cardiac index, Qp/Qs, pulse oximetry, and hemoglobin were not significantly

changed, but brain natriuretic peptide and NYUPHFI improved significantly. After bosentan therapy, 3 patients underwent bidirectional Glenn surgery and all 8 patients successfully underwent Fontan surgery (Table 3).

After the Fontan operation, all patients continued bosentan therapy. However, 2 patients (numbers 1 and 2) were admitted to the hospital once because of protein-losing enteropathy, but they recovered completely with heparin therapy (Tables 2 and 3). The remaining 6 patients had no complications, including protein-losing enteropathy, plastic bronchitis, and liver dysfunction. The average NYUPHFI score in the 8 patients improved to 6.0 ± 0.5 after Fontan surgery.

Safety and Tolerability

All patients maintained adequate serum bosentan concentrations during therapy (Table 5). As we administered initial doses of bosentan adjusting for patients' body weight, tachypnea and chest discomfort did not occur in any of the patients. Abnormal hepatic function, interference with the international normalized ratio, and other adverse events were not observed in this study.

DISCUSSION

We show that bosentan therapy reduces PAP and PVR in patients with SV physiology who are unable to undergo right-sided heart bypass surgery because of high PVR and PAP. With the support of bosentan therapy, the bidirectional Glenn procedure was performed in 3 cases, and the Fontan operation was completed successfully in all 8 cases.

TABLE 3. Palliative surgery before bosentan and latest operations after bosentan

Patients	Diagnosis	Age	Prior operation	Starting age of bosentan	Age	After bosentan therapy
1	Asplenia, SV, DORV, CoA, TAPVR	2 d	CoA repair, PAB	9 mo	1 y	BDG
		23 d	re-PAB		2 y	Fontan
		7 mo	re-re-PAB			
		8 mo	TAPVR repair			
2	Asplenia, SV, MA, DORV, TAPVR	1 mo	PAB	8 mo	11 mo	BDG
		2 mo	TAPVR repair		2 y	Fontan
3	Asplenia, SV, DORV, PS, TAPVR	19d	TAPVR repair	1 y	2 y	BDG
		1 y	Right modified BT shunt		3 y	Fontan
4	Asplenia, SV, CAVC, DORV, PS, TAPVR	2 mo	CAVVP	7 mo	2 y	Fontan
		1 y	BDG			
5	HLHS	2 d	PTAV	10 mo	2 y	Fontan
		15 d	Bilateral PAB			
		4 mo	Norwood, MVP			
		8 mo	Right BDG, intrapulmonary artery septation*			
6	HLHS	7 d	Norwood	2 y	2 y	Fontan
		7 mo	BDG			
7	HLHS	8 d	Norwood	5 y	6 y	Fontan, CRT†
		8 mo	Left modified BT shunt			
		1 y	Right modified BT shunt			
		2 y	BDG			
		2 y	PMI			
8	SV, DORV, d-MGA	1 mo	PAB	1 y	2 y	DKS, Fontan
		7 mo	BDG, ASD enlargement, re-PAB			

SV, Single ventricle; DORV, double outlet right ventricle; CoA, coarctation of aorta; TAPVR, total anomalous of pulmonary venous return; MA, mitral atresia; PS, pulmonary stenosis; PAB, pulmonary artery banding; CAVC, complete atrioventricular canal; HLHS, hypoplastic left heart syndrome; d-MGA, d-malposition of the great arteries; CAVVP, common atrial ventricular valvular plasty; BDG, bidirectional Glenn; PTAV, percutaneous transluminal balloon aortic valvuloplasty; MVP, mitral valvular plasty; BT, Blalock–Taussig; PMI, pacemaker implantation; ASD, atrial septal defect; CRT, cardiac resynchronization therapy; DKS, Damus–Kaye–Stansel. *Patient 4 had intrapulmonary artery septation and right BDG caused by left pulmonary artery stenosis. The flow of the superior vena cava was connected to the right pulmonary artery, and the flow of the left pulmonary artery was supplied by the right ventricular pulmonary artery shunt.²⁴ †Patient 7 had dysrhythmia and heart failure caused by ventricular dyssynchrony before the Fontan operation. Cardiac resynchronization therapy was performed with Fontan operation.

Elevated PAP greater than 18 to 20 mm Hg and PVR greater than 3 or 4 Woods units are known risk factors for death or failure of anastomosis in patients with bidirectional Glenn shunts.^{14,15}

Endothelin has been implicated in the pathogenesis of pulmonary hypertension secondary to CHD. Endothelin mediates vasoconstriction and induces vascular smooth muscle cell contraction, proliferation, and inflammation. Increased

TABLE 4. Hemodynamic parameters before and after bosentan treatment

	Non-PAH group (n = 20)	Before bosentan treatment (n = 8)	After bosentan treatment (n = 8)	Percentage change (%)	P value
Body weight (kg)	7.3 ± 1.2	7.1 ± 1.8	9.1 ± 2.1	+27.9	.0088
Body surface area (m ²)	0.36 ± 0.05	0.34 ± 0.09	0.45 ± 0.09	+32.4	.0171
Main mean PAP (mm Hg)	12.4 ± 4.1	21.1 ± 7.2	11.9 ± 4.1	−43.8	.0014
PVR (U/m ²)	1.50 ± 0.57	5.72 ± 3.34	1.30 ± 0.43	−77.3	.0035
PVR/SVR	0.08 ± 0.02	0.25 ± 0.11	0.07 ± 0.03	−72.0	.0009
PA index	412 ± 154.0	237 ± 119.2	242.1 ± 81.6	+2.0	.4180
Cardiac index (L/min/m ²)	3.36 ± 0.80	3.59 ± 1.12	3.16 ± 1.05	−12.0	.1962
Qp/Qs	1.47 ± 0.60	0.93 ± 0.44	1.06 ± 0.42	+14.0	.2286
Hb (g/dL)	15.6 ± 1.3	15.3 ± 1.4	15.5 ± 2.6	+1.0	.4266
Pulse oxymetry (%)	79.6 ± 5.7	77.9 ± 5.6	83.5 ± 4.8	+7.2	.0164
BNP (pg/mL)	123.4 ± 253.1	221.5 ± 189.6	65.4 ± 70.9	−70.5	.0367
NYUPHFI score	5.6 ± 1.6	10.5 ± 2.3	8.0 ± 2.4	−23.8	.0026

PAH, Pulmonary artery hypertension; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PA, pulmonary artery; Qp, pulmonary blood flow; Qs, systemic blood flow; Hb, hemoglobin; BNP, brain natriuretic peptide; NYUPHFI, New York University Pediatric Heart Failure Index. Data are mean ± standard deviation. P value is derived from comparison of before and after bosentan treatment.

TABLE 5. Dosage and side effects of bosentan

Patient	Duration	Dosage (mg/kg/d)	Concentration (trough) (ng/mL)	Concentration (peak) (ng/mL)	Adverse effect
1	1 y	1	27.6	78.6	None
2	1 y	2	27.5	76.6	None
3	1 y	2	102.1	522.8	None
4	10 mo	2	17.3	136.1	None
5	8 mo	3	55.8	704.0	None
6	1 y	2	52.3	365.8	None
7	7 mo	3	187.2	220.6	None
8	6 mo	2	147.3	399.4	None

levels of endothelin-1 have been found in plasma and lung biopsies of patients with CHD and PAH.^{16,17} Elevated PAP and excessive pulmonary flow have been associated with elevated endothelin-1 levels in experimental models and in patients with CHD.^{18,19}

The use of bosentan in pediatric patients was evaluated in a prospective, open-label pharmacokinetic study in 19 children with idiopathic PAH or PAH related to CHD.²⁰ Bosentan treatment for 12 weeks resulted in hemodynamic improvement and formed the basis of the current dosing schedule for the drug in pediatric patients.²⁰ In a retrospective study of 86 pediatric patients primarily with idiopathic PAH or PAH related to CHD, bosentan improved or maintained World Health Organization functional class and improved hemodynamics.²¹ Kaplan–Meier estimates of survival at 1 and 2 years were 98% and 91%, respectively. In another retrospective study of 40 pediatric patients, bosentan helped stabilize children with idiopathic PAH, but intravenous epoprostenol was also needed by 60%. Children with PAH related to other conditions improved.²²

It has been reported that plasma endothelin-1 is elevated and adrenomedullin is decreased after Fontan operations, and an imbalance between endothelin-1 and adrenomedullin might induce vasoconstriction.²³ There was a positive correlation between endothelin-1 levels and PVR.²³ Although we did not examine the serum level of endothelin, the bosentan doses used in this study were efficacious and of benefit to patients with Fontan circulation.

These results suggest that bosentan may induce hemodynamic improvement in patients with SV physiology with decreased PVR and PAP, thus increasing the surgical options. Further, endothelin may play an important role in maintaining vasoconstriction in SV physiology before and after right-sided heart bypass surgery.

Study Limitations

Within a few months of starting bosentan therapy, some of our patients had surgical procedures that may have had slowly developing favorable effects on PVR. However, catheterization data before starting bosentan showed fixed

elevated PVR even on hyperoxia or vasodilator challenge, so favorable effects on PVR cannot be explained only by delayed effect of before surgical procedures. Our study was limited to a small number of patients. Larger, placebo-controlled studies with long-term administration of bosentan are needed to assess the optimal doses and possible therapeutic role of bosentan in this patient population.

CONCLUSIONS

Bosentan therapy reduced PAP and PVR and improved clinical symptoms and exercise tolerance in all cases. Bosentan induced mid-term clinical and hemodynamic improvement in patients with SV physiology with increased PVR. Bosentan therapy may increase the surgical options and improve the outcome in Fontan candidates with increased PVR secondary to diminished pulmonary vasculature and relative pulmonary overcirculation.

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