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Bosentan Is Associated with a Reduction in Right Ventricular Systolic Pressure N-Terminal Pro-Hormone B-Type Natriuretic Peptide Levels in Young Patients with Pulmonary Hypertension

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Abstract

Pulmonary hypertension is a rare and potentially fatal disease in children if left untreated. Emerging therapies, including Bosentan, a dual endothelin receptor antagonist, have shown significant benefits in the adult pulmonary hypertension population; however, few studies have assessed the efficacy and safety of endothelin receptor antagonists in infants and young children. Our study was a single-center retrospective analysis of patients less than two years of age with a confirmed diagnosis of pulmonary hypertension and initiated on Bosentan therapy between 2017 and 2020. Twelve cases met eligibility criteria. Demographic data, laboratory data, echocardiographic, and cardiac catheterization data were analyzed. With treatment, there was a statistically significant decrease in mean right ventricular systolic pressure estimated by the tricuspid regurgitation jet (79 ± 23 mmHg reduced to 52 ± 25 mmHg; $p < 0.001$) N-terminal pro-hormone B-type natriuretic peptide levels (21,071 reduced to 2,037; $p < 0.001$). Additionally, improvement and eventual normalization of right ventricular function and septal geometry was seen within the first four months of therapy. Patients who underwent cardiac catheterization after therapy initiation ($n = 4$) demonstrated hemodynamic improvements; however, only the decrease in diastolic pulmonary artery pressure was statistically significant ($p = 0.018$). No significant differences in hemoglobin, platelet count, or liver function tests were observed between groups. In con-

clusion, these data suggest that Bosentan may be an effective and relatively safe treatment option for children less than two years of age with pulmonary hypertension. Further long-term randomized control studies are necessary to validate the potential clinical benefit of utilizing this drug therapy in young children.

Keywords

Pulmonary Arterial Hypertension, Bronchopulmonary Dysplasia, Endothelial Receptor Antagonist, Congenital Heart Disease

1. Introduction

Pulmonary hypertension is a rare disease in children that is characterized by a series of vascular changes that result in increased pulmonary vascular resistance and eventually right heart failure [1] [2] [3]. Despite varying etiologies, pulmonary hypertension in the pediatric age group carries a poor prognosis if left untreated [2] [4] [5] [6] [7]. Significant therapeutic advances have been made over the past several decades; this is due in part to an improved understanding of the mechanisms involved in the pathogenesis of this disease. Current treatment options target one of three pathways: the nitric oxide pathway, the endothelin pathway, or the prostacyclin pathway [2] [3] [8] [9] [10].

Bosentan is an oral dual endothelin receptor antagonist that inhibits endothelial cell proliferation by binding to receptors on endothelial cells of vascular smooth muscle and inhibiting endothelin-1 activity [1] [3]. The clinical benefits of utilizing Bosentan to treat adult pulmonary hypertension are well-demonstrated in the literature [11] [12] [13]; however, data evaluating the efficacy of Bosentan therapy in children are minimal [1] [2] [3] [14]. The Bosentan Randomized trial of Endothelin Antagonist Therapy (BREATHE-3) pharmacokinetic trial was the first open-label study to assess the effects of Bosentan in pediatric patients [15]. Study results demonstrated hemodynamic improvements with therapy and revealed a clinical safety and efficacy profile comparable to that previously observed in adult patients [14] [15].

In 2017, the US Food & Drug Administration approved Bosentan to treat pulmonary arterial hypertension (World Health Organization Group 1) in pediatric patients aged three years and older [1] [16]. Since then, endothelial receptor antagonists by themselves or in combination with prostanoid therapy, have become an attractive option for treating pediatric pulmonary hypertension. Despite this trend, very few studies have looked at the effects of Bosentan and other endothelin receptor antagonists in children who are less than three years of age.

This retrospective analysis was designed with the objective to assess the efficacy of Bosentan therapy for the treatment of pulmonary hypertension (World Health Organization Groups 1 and 3) in children less than two years of age. We

hypothesized that Bosentan added to Sildenafil therapy for this age group would be both safe and effective. Additionally, we hypothesized that the addition of Bosentan would result in improved right ventricular pressure estimates, intraventricular septal geometry, pulmonary vascular resistance, and N-terminal pro-hormone B-type natriuretic peptide levels (NT-proBNP).

2. Methods

2.1. Design and Case Selection

This retrospective chart review was conducted at a single-center university hospital in Jackson, Mississippi. After receiving approval from the University of Mississippi Institutional Review Board, data was collected on all pediatric patients less than two years of age that had a confirmed diagnosis of pulmonary hypertension that were subsequently started on Bosentan therapy between January 1, 2017 and March 1, 2020. This group included patients with pulmonary hypertension due to bronchopulmonary dysplasia (World Health Organization Group 3), pulmonary arterial hypertension associated with congenital heart disease (World Health Organization Group 1), and persistent pulmonary hypertension of the newborn (World Health Organization Group 1). The diagnosis of pulmonary hypertension was confirmed by either echocardiography or right heart catheterization. Patients greater than two years of age were excluded from this study. Patients meeting the above criteria were identified from an internal hospital pharmacy database.

2.2. Treatments

At our institution, oral Sildenafil was considered first-line treatment for patients with newly diagnosed pulmonary hypertension. All patients included in this study were on a stable dose of Sildenafil for an average of six months prior to the initiation of Bosentan. The starting dose for oral Sildenafil was 0.5 milligrams (mg)/kilogram (kg)/dose given every eight hours. This dose was titrated as tolerated to a target of 1 mg/kg/dose given every eight hours. Patients were started on Bosentan of 1 mg/kg/dose every twelve hours. This dose was then titrated up after four weeks to 2 mg/kg/dose every 12 hours.

2.3. Data Extraction and Outcome Measures

All information was collected via patients' electronic medical records and was entered into a Research Electronic Data Capture (REDCap) database (University of Mississippi Medical Center, Jackson, MS) to ensure data security [17] [18]. Demographic data, primary and secondary diagnoses, laboratory data, echocardiographic data, and hemodynamic cardiac catheterization data were recorded.

Echocardiographic data, cardiac catheterization, and NT-proBNP data were used to assess treatment efficacy. NT-proBNP levels were drawn prior to initiation of Bosentan therapy and then trended at monthly intervals for a total of twelve months.

Echocardiographic data was obtained from standardized echocardiography reports. These structured reports were prepared by various in-house pediatric cardiologists utilizing syngo Dynamics imaging software (version VA40C). Echocardiographic images were obtained in a similar fashion, utilizing a standardized pediatric echocardiography protocol. Qualitative measures including interventricular septal configuration and right ventricular function were recorded. Additionally, quantitative measures including left ventricular ejection fraction (using 2D M-mode method) and right ventricular systolic pressure estimates were also recorded. Specifically, the peak velocity of the tricuspid regurgitation jet was utilized to estimate the right ventricular systolic pressure. If the tricuspid regurgitation jet was considered inadequate for the purpose of estimating right ventricular systolic pressure, no value was recorded. Baseline echocardiograms were obtained at the time of diagnosis and then at monthly intervals after treatment initiation for a twelve-month period. If available, cardiac catheterization data including direct measurement of mean pulmonary artery pressure, diastolic pulmonary artery pressure, indexed pulmonary vascular resistance, indexed systemic vascular resistance, pulmonary vascular resistance to systemic vascular resistance ratio, transpulmonary gradient, and diastolic pulmonary gradient were collected.

Liver function tests and complete blood counts, both adjusted for age, were used to assess end-organ function and to evaluate treatment safety. Baseline laboratory values were obtained prior to initiation of Bosentan therapy and trended monthly for twelve months. The need for treatment discontinuation due to adverse side effects was also recorded.

2.4. Statistical Methods

The Statistical Product and Service Solutions (IBM SPSS statistics for windows version 27 Armonk, NY: IBM Corp) was used to analyze the data. A two-tailed independent T-test was used to analyze continuous variables between the groups. Pearson chi-square (chi-squared goodness-of-fit test) and Fischer exact test were used for categorical values and dichotomous response variables (frequency comparisons). An alpha of 0.05 was used to determine significance.

3. Results

The study group included twelve patients diagnosed with pulmonary hypertension between the ages of 0.2 and 7.2 months (mean age 3.6 months) that were started on Bosentan. Demographic characteristics are shown in Table 1. The majority of patients had pulmonary hypertension due to bronchopulmonary dysplasia (42%). Less common diagnoses were persistent pulmonary hypertension of the newborn (33%) and pulmonary arterial hypertension associated with congenital heart disease (25%). Specific cardiac lesions included the following: complete atrioventricular septal defect, partial anomalous venous drainage or

Table 1. Descriptive statistics.

Patients' Characteristics	Patients (n = 12)	
Male	9	(75%)
Female	3	(25%)
Gestational age at birth (weeks)	31.8 ± 6 [23.4 - 40]	
Birth weight (g)	1759 ± 1106 [660 - 3580]	
Ethnicity		
African American	7	(58%)
Caucasian	5	(42%)
Etiology of PH		
PH associated with bronchopulmonary dysplasia	5	(42%)
PAH associated with CHD	3	(25%)
PPHN	4	(33%)
Age at diagnosis (months)	3.6 ± 2.4 [0.2 - 7.2]	
Age at time of Bosentan initiation (months)	9.6 ± 4.4 [3 - 17.8]	
Time from diagnosis to initiation of Bosentan therapy (months)	6.0 ± 5.2 [0.3 - 17.8]	
ICU survival	7	(58%)
Hospital survival	7	(58%)

Note. Data are shown as n (%), mean ± standard deviation [range]. PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; CHD = congenital heart disease; PPHN = persistent pulmonary hypertension of the newborn; ICU = intensive care unit.

Scimitar syndrome, and large ostium seccundum atrial septal defect associated with Holt-Oram syndrome. Patients ranged in age from 3 months to 17.8 months (9.6 ± 4.4 months; mean ± SD) at the start of Bosentan therapy with drug initiation occurring, on average, 6 months (6.0 ± 5.2 months; mean ± SD) from the time of diagnosis.

All twelve patients had echocardiographic assessments preceding Bosentan initiation and eleven out of the twelve patients had at least one follow-up assessment. One patient expired prior to receiving a follow-up echocardiographic assessment. Baseline and post-treatment echocardiographic parameters are listed in Table 2. Overall, there was a significant improvement in qualitative right ventricular function assessment and septal geometry pattern following treatment with Bosentan. Six of the twelve patients (50%) in the pre-treatment group had echocardiographic evidence of mild-to-moderate right ventricular dysfunction at baseline, in comparison to the post-treatment group, which had none (100% had normal right ventricular function). Regarding septal geometry, five patients (42%, n = 12) in the pre-treatment group had an interventricular septal configuration suggestive of suprasystemic right ventricular systolic pressure (bowing to the left ventricle), in comparison to the post-treatment group, which had zero

Table 2. Change in Echocardiographic, catheterization, and laboratory parameters with treatment.

Echocardiographic Parameters	Baseline (n = 12)	Post-treatment (n = 11*)	P-value	
Right ventricular function				
Normal	6 (50%)	11 (100%)	0.04	
Mildly depressed	4 (33%)	0 (0%)	<0.01	
Moderately depressed	2 (17%)	0 (0%)	<0.01	
Interventricular septal position				
Normal	0 (0%)	4 (36%)	0.09	
Flattened septum	7 (59%)	7 (64%)	1.00	
Bowing into the left ventricle	5 (42%)	0 (0%)	0.04	
RVSP from TR (mmHg)	79 ± 23 [40 - 120]	52 ± 25 [23 - 100]	<0.001	
Left ventricular ejection fraction (%)	77 ± 10 [58 - 88]	71 ± 9.6 [59 - 88]	0.50	
Catheterization Parameters	**Baseline (n = 7)**	**Post-treatment (n = 4)**	**P-value**	**95% CI**
PVRI (Wood units × m^2)	5.06	3.14	0.140	−0.77 - 4.62
SVRI (Wood units × m^2)	10.7	11.4	0.811	−7.80 - 6.27
PVR/SVR ratio	0.54	0.34	0.253	−0.17 - 0.57
MPAP (mmHg)	34.4	31.0	0.443	−5.67 - 12.9
DPAP (mmHg)	21.0	16.0	0.018	1.06 - 8.94
Transpulmonary gradient (mmHg)	23.7	18.7	0.183	−2.79 - 12.8
Diastolic pulmonary gradient (mmHg)	9.5	7.0	0.403	−3.87 - 8.87
Laboratory Parameters	**Baseline (n = 12)**	**Post-treatment (n = 12)**	**P-value**	**95% CI**
NT-proBNP	21071	2037	<0.001	4655 - 33413
Hemoglobin	11.09	11.95	0.161	−2.07 - 0.36
Platelet count	269.75	259.24	0.732	−51.3 - 72.3
Aspartate transaminase	52.1	45.54	0.359	−7.78 - 20.9
Alanine aminotransferase	43.3	32.96	0.137	−3.46 - 24.1

Note. Data are shown as either n (%), mean ± standard deviation [range], or mean values. NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation jet; PVRI = indexed pulmonary vascular resistance; SVRI = indexed systemic vascular resistance; PVR/SVR = pulmonary vascular resistance to systemic vascular resistance ratio. MPAP = mean pulmonary artery pressure; DPAP = diastolic pulmonary artery pressure. CI = confidence interval. *One patient expired prior to getting a post-treatment echocardiogram.

patients (n = 11) with interventricular septal configurations suggestive of supra-systemic right ventricular systolic pressure ($p \leq 0.04$). On average, right ventricular function improved after 1.6 months of therapy and normalized after 2 months of therapy. Intraventricular septal configuration improved after an av-

erage of 2.7 months of therapy and normalized after an average of 3.8 months after therapy.

Additionally, a statistically significant improvement in mean estimated right ventricular systolic pressure was demonstrated (p-value < 0.001) (Table 2). The mean estimated right ventricular systolic pressure by tricuspid regurgitation jet decreased from 79 ± 23 mmHg (mean ± SD) to 52 ± 25 mmHg (mean ± SD) following treatment (p-value < 0.001). There was no significant difference in left ventricular ejection fraction between groups.

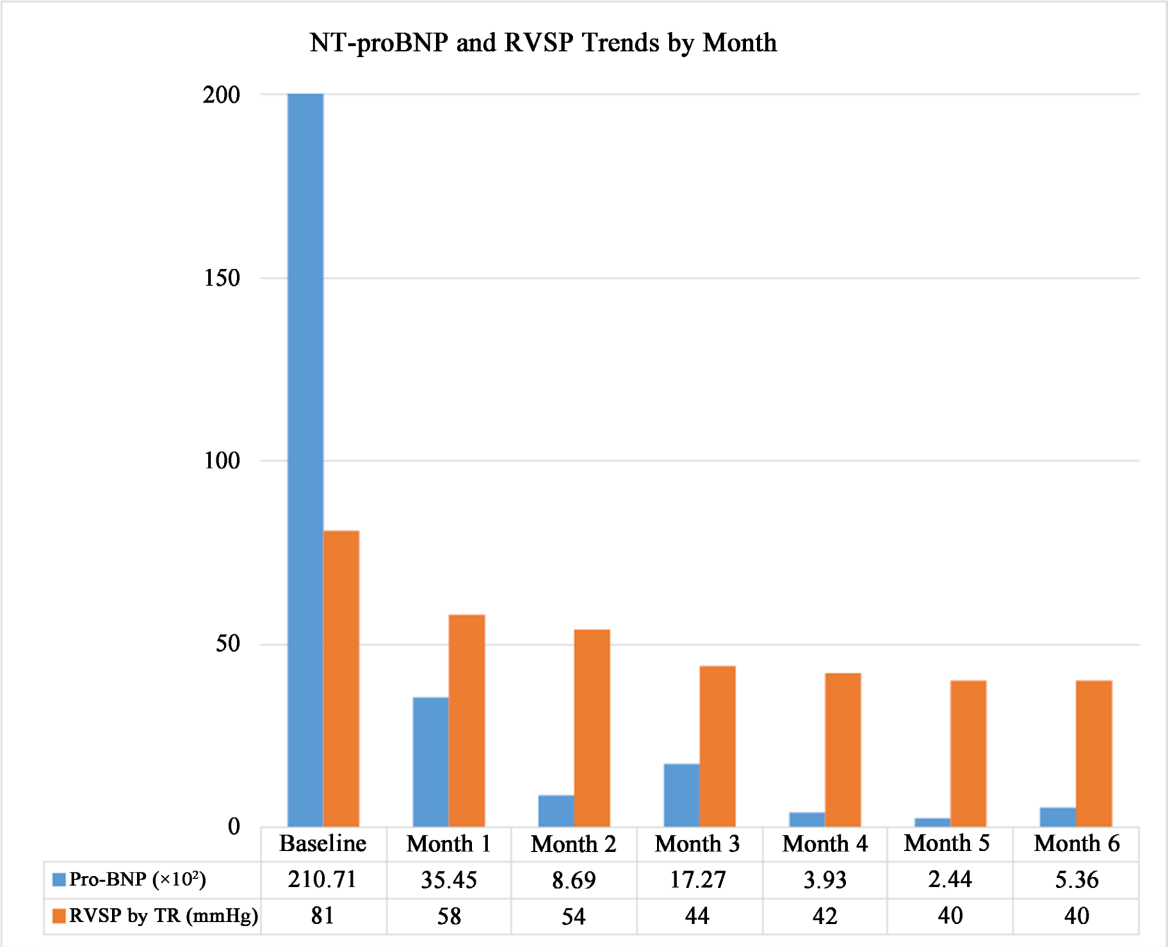
Seven of the twelve patients had a hemodynamic cardiac catheterization assessment prior to starting Bosentan therapy. Of those seven, four underwent follow-up assessment. Baseline and post-treatment catheterization parameters are listed in Table 2. Aside from a reduction in the diastolic pulmonary artery pressure with treatment (95%CI: 1.06 - 8.94; p-value 0.018), there was no statistically significant change in mean pulmonary artery pressure, diastolic pulmonary pressure, transpulmonary gradient, indexed pulmonary vascular resistance, or pulmonary vascular resistance to systemic vascular resistance ratio in the post-treatment group (n = 4). There was a slight increase in the indexed systemic vascular resistance from 10.7 indexed Wood units to 11.4 indexed Wood units after treatment.

Baseline laboratory data was obtained and trended monthly on all twelve patients. Changes in laboratory data in the pre and post-treatment groups are listed in Table 2. There was a statistically significant decrease in mean NT-proBNP levels from 21,071 to 2037 with treatment (p < 0.001). Mean NT-proBNP and right ventricular systolic pressure monthly trends are shown in Figure 1. The greatest decline in mean NT-proBNP levels and mean estimated right ventricular systolic pressure occurred within the first month of treatment. Mean NT-proBNP levels decreased by 83.2% within the first month, and mean estimated right ventricular systolic pressure decreased by 28% within the first month. There was no significant difference in hemoglobin, platelet count, aspartate transaminase, or alanine transaminase levels between groups (Table 2).

4. Discussion

Pediatric pulmonary hypertension is a life-threatening illness that requires early diagnosis and prompt medical treatment. Despite recent advances in disease-targeted therapies, there remains an enormous amount of variability in clinical practice regarding treatment strategy [19]. This is likely attributed to the paucity of clinical research in children and lacking number of pediatric-specific pharmacologic trials.

In an effort to help guide care for these tenuous patients, several comprehensive diagnostic and treatment algorithms have developed over the years. These algorithms are predominantly based on expert opinion, not clinical evidence [19] [20] [21] [23] [24]. The Pediatric Task Force of the 6th World Symposium on Pulmonary Hypertension released an updated management algorithm in 2018,



Note: NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation jet.

Figure 1. N-Terminal Pro-Hormone B-Type Natriuretic Peptide and Right Ventricular Systolic Pressure Trends by Month.

recommending oral therapies such as ERAs, phosphodiesterase type 5 inhibitors, and prostacyclin analogs (oral or inhaled) for the treatment of low-risk patients, either as a single agent or in combination [19] [21].

In recent years, efforts have aimed to legitimize these treatment recommendations with clinical evidence [21] [22] [25]. Several pediatric studies have demonstrated the clinical utility of Bosentan therapy for the treatment of pediatric pulmonary hypertension, including improvement in survival, hemodynamics, World Health Organization functional class, and 6-minute walking distances [1] [3]. However, it is worth noting that the majority of these study participants included older children and adolescents, making our study one of only a few pediatric cohort studies to evaluate the efficacy of Bosentan use in infants and children who are less than two years of age.

Specific to this younger patient population, our study demonstrated a statistically significant improvement in echocardiographic and laboratory screening parameters after initiating Bosentan therapy in patients with pulmonary hyper-

tension who had previously been on a stable dose of Sildenafil. Specifically, we saw a significant improvement in mean estimated right ventricular systolic pressure (estimated by the tricuspid regurgitation jet), right ventricular function, septal geometry patterns, and NT-proBNP levels in as early as one month after therapy initiation. In contrast to previously-conducted studies, we did not see a significant change in hemodynamics with therapy; however, this is likely attributed to the limited amount of catheterization data.

Regarding safety, Bosentan carries a known potential risk for dose-dependent increases in amino transaminase levels, and Sildenafil has a potential risk for anemia [3]. Specifically, we did not observe any significant change in hemoglobin, platelet count, or liver function tests following treatment initiation. This data suggests that Bosentan in combination with Sildenafil is a relatively safe treatment option for infants and children less than two years of age.

Our study certainly has limitations; the most significant being the retrospective nature of the study, and the inability to definitively establish true cause-and-effect relationships. Furthermore, this was a single-center study with a small sample size, limiting the overall power. With a retrospective analysis, some data may be incomplete or inaccurate. As previously mentioned, very few of our patients underwent a hemodynamic cardiac catheterization prior to or after the initiation of Bosentan therapy, making it difficult to make an accurate assessment of hemodynamics. Additionally, measures derived from echocardiography are to some extent operator and interpreter-dependent, allowing for a small degree of interpretation bias. More quantitative methods of assessing right ventricular function such as tricuspid annular plane systolic excursion and myocardial performance index were not yet incorporated into the echocardiography protocol that was utilized during the study period. Lastly, because all of our patients had been receiving a stable dose of Sildenafil for several months prior to starting Bosentan therapy, we are unable to determine if upfront combination therapy may be more or less beneficial. We are also unable to determine if alternative combination therapies, such as Bosentan combined with a different phosphodiesterase inhibitor, such as Tadalafil, would have a similar effect.

In conclusion, these data suggest that Bosentan may be an effective and safe treatment option for children less than two years of age with pulmonary hypertension. Further long-term randomized control studies are necessary to validate the potential clinical benefit of utilizing this drug therapy in young infants and children. Additionally, further clinical studies looking at specific drug combinations are needed to continue to strengthen our treatment strategies for this very fragile patient population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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