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Original Research Article

Bosentan-sildenafil combination in the treatment of patients with severe pulmonary hypertension, and its effect on cardiac function

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Abstract

Purpose: *To study the efficacy of bosentan combined with sildenafil in the treatment of severe pulmonary hypertension (PH), and its impact on cardiac function.*
Methods: *In total, 90 severe PH patients treated in The First Affiliated Hospital of Harbin Medical University, Harbin, China between November 2018 and November 2019 were included and equally assigned to two groups (A and B). Group A was treated with bosentan combined with sildenafil, while group B received conventional treatment, viz, deslanoside injection followed later by 40 mg furosemide intravenous injection. Clinical efficacy, sleep quality, psychological status, and cardiac function for the two groups were compared.*
Results: *Group A had significantly higher effectiveness than group B before treatment ($p < 0.05$). Similar Pittsburgh Sleep Quality Index (PSQI) scores before treatment between the two groups were found ($p > 0.05$). After treatment, group A had a lower PSQI score than group B ($p < 0.001$). Also, following treatment, group A had more level I patients and fewer level III patients than group B ($p < 0.05$). The Beck depression rating scale (BDI) scores at T0 and T1 were similar for the two groups ($p > 0.05$). Lower post-treatment BDI scores in group A at T2 and T3, than in group B were observed ($p < 0.001$). In contrast to the conventional treatment group, group A had a higher cardiac output and higher cardiac index, lower systemic arterial pressure, and lower incidence of adverse reactions ($p < 0.05$).*
Conclusion: *Bosentan combined with sildenafil produces higher therapeutic effects on severe PH patients than conventional treatment.*

Keywords: *Bosentan, Sildenafil, Severe pulmonary hypertension, Cardiac function*

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INTRODUCTION

Pulmonary hypertension (PH), an increase in pressure in blood vessels from the heart to the lungs, is a complication of heart failure [1,2]. It often presents with fatigue, shortness of breath and angina pectoris after physical activity. In severe cases, PH may result in heart failure with poor clinical prognosis. In clinical practice, PH is defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest via right heart catheterization at sea level [3].

The most common cause of PH is left ventricular disease, with lung disease and hypoxia as the other causes [4]. Therefore, there is need for development of PH drugs for improving the prognosis of the disease and reducing its associated mortality. Endothelin 1 (ET-1) is currently the most potent endogenous vasoconstrictor known. It acts on pulmonary arteriole smooth muscle cells through endothelin receptors. Endothelin-1 (ET-1) enhances proliferation, fibrosis, and contraction of blood vessels, and is expressed at high levels in the lung tissue and plasma of PH patients [5,6]. Thus, endothelin receptor antagonists (ERAs) are regarded as promising treatments for PH and the associated heart failure.

Bosentan is a non-peptide non-selective endothelin receptor antagonist, and acts by reducing vascular pressure-induced pulmonary fibrosis and inflammation [7]. Sildenafil is a selective inhibitor which relaxes the smooth muscles of the pulmonary blood vessels and promotes vascular remodeling [8]. Thus, presumably, the clinical symptoms of PH may be mitigated by combined use of these two drugs, since each drug has failed in clinical practice when used alone for treating PH. This study was conducted to evaluate the treatment efficiency of bosentan combined with sildenafil for severe PH.

METHODS

General profile of patients

This study involved 90 matched, severe PH patients who received treatment in our hospital between November 2018 and November 2019. The present study was authorized by the Ethics Committee of First Affiliated Hospital of Harbin Medical University (approval no. 2018063010) [9], and followed international guidelines for human studies.

Inclusion criteria

All patients signed informed consent form. The patients in this study were aged 20-80 years, diagnosed as idiopathic or familial PH, and belonged to New York Heart Association (NYHA) functional class II or III severity, with a baseline 6-min walk distance (6MWD) from 213 to 420 meters. They were distributed to groups A and B based on left ventricular ejection fraction (LVEF). Patients enrolled in this research had no history of congenital heart disease, cancer, HIV infection, smoking, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, connective tissue disease, or sarcoidosis.

Patients in the following categories were enrolled in the study: (1) patients who satisfied the clinical diagnostic criteria for PH in the American Heart Association (AHA) guidelines; (2) patients with data for pre-capillary and post-capillary PH measured and indicated as mean PAP (mPAP); those with mPAP > 70 mmHg, pulmonary vascular resistance (PVR) > 3 WU, and LVEF > 30 %; and (3) patients who had not received clinical treatment immediately before the study. The patients and families were informed of the purpose and processes of the study, and signed informed consent forms.

Exclusion criteria

Patients with unstable clinical conditions, congenital diaphragmatic hernia, lung disease, heart disease, allergies to the drugs used, mental or other cognitive impairments, and poor compliance, were excluded.

Treatments

Group B patients received routine clinical treatment, viz, deslanoside injection (Shanghai Xudong Haipu Pharmaceutical Co. Ltd. Specification: 2 mL: 0.4 mg × 2 bottles/box; NMPA approval number: H31021178). The drug was diluted in 5 % glucose injection solution. The first doses were 0.4 - 0.6 mg, and doses of 0.2 - 0.4 mg were given every 2 – 4 h. The total doses were 1.0 - 1.16 mg. Then, 40 mg furosemide was injected intravenously (Henan Runhong Pharmaceutical Co. Ltd; NMPA approval number: H41020310 Specification: 20 mg/2 mL) to maintain body electrolytes, 2 times/day.

Patients in group A were given bosentan in combination with sildenafil. The patients took sildenafil (Guangzhou Baiyunshan Pharmaceutical Group Co. Ltd; NMPA Approval Number: H20143255; Baiyunshan General Pharmaceutical Factory Specification: 50 mg x 6 s) at a dose of 25 mg thrice daily. Group A patients also received bosentan (Canadian Patheon Inc; NMPA Approval Number: H20170013; Specification: 125 mg x 56 tablets), at a dose of 62.5 mg 2 times/day. Both groups of patients were treated continuously for 10 days.

Parameters measured

The efficacy analysis was conducted 3 days after the end of treatment. Treatment efficacy in terms of change in mPAP was categorized as *significantly effective* if the clinical symptoms of the patient were significantly improved after treatment, or *effective* if various clinical symptoms were mitigated, or i*neffective* if there

were no signs of improvement in the condition of the patient or if the conditions got even worse. Total effectiveness was obtained by summation of significantly effective cases and effective cases.

The Pittsburgh sleep quality index (PSQI) was employed to assess the sleep conditions of the patients before and after treatment. The scale has 7 scoring factors and a total score of 21 points. The score is adversely proportional to the quality of sleep.

The heart function of patients after treatment was evaluated according to the "New York Cardiac Function Classification Standard". This standard categorizes cardiac function into different levels viz: Level I is for patients who have no restrictions on daily activities, no palpitations, no asthma, and no angina after general physical activity. In Level II patients, daily activities are slightly restricted, and fatigue, angina, and asthma may occur after normal activities, except when the patients are at rest. Level III is for patients whose daily physical activities are restricted because such activities result in excessive fatigue, heart palpitations and asthma, in addition to other problems.

The "Borg Dyspnea Scale" (BDI) was employed to evaluate the degree of dyspnea in patients at different times. The time points were before treatment, 3 days after treatment, 5 days after treatment, and 10 days after treatment. These were designated T0, T1, T2 and T3, respectively. In the BDI scale, the higher the score, the more difficult it is for the patient to breathe.

The cardiac output, cardiac index, and systemic arterial pressure of the two groups after treatment were measured using right heart catheterization 1 day after final treatment.

The incidence of clinically adverse reactions of the patients were calculated.

Statistical analysis

The experimental data were statistically analyzed and processed with SPSS version 21.0 software, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was employed to prepare graphics and charts. Count data are presented as numbers and percentages [n (%)], and analyzed with chi square (χ^2) test. Measurement data are expressed as mean ± standard deviation (SD), and processed with *t*-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Basic patient profile

Table 1 shows similar general data such as sex, mean age, mean BMI value, mean mPAP, combined underlying diseases, educational level, and places of residence between the two groups ($p > 0.05$).

Table 1: Comparison of clinical data between the two groups

Parameter	Group A (n=45)	Group B (n=45)	χ^2/t	*P*-value
Sex			0.046	0.830
Male	27（60.00%）	26（57.78%）		
Female	18（40.00%）	19（42.22%）		
Mean age (years)	52.25±3.57	52.28±3.49	0.040	0.968
Mean BMI (kg/m^2)	21.24±1.27	21.28±1.31	0.147	0.883
Mean mPaP (mmHg)	86.52±9.21	86.56±9.24	0.021	0．984
LVEF			0.052	0.875
<50%	12 (26.67%)	11 (24.44%)		
≥50%	33 (73.33%)	34 (75.56%)		
Combined underlying diseases			0.045	0.832
Congenital heart disease	23 (51.11%)	21 (46.67%)	0.039	0.973
Hypertension	25（55.56%）	24（53.33%）		
Diabetes	20（44.44%）	21（46.67%）		
Education level				
Undergraduate	11（24.44%）	13（28.89%）	0.227	0.634
Middle school	18（40.00%）	19（42.22%）	0.046	0.830
Primary school	16（35.56%）	13（28.89%）	0.458	0.499
Place of residence			0.048	0.827
Urban area	17（37.78%）	16（35.56%）		
Rural area	28（62.22%）	29（64.44%）		

Table 2: Comparison of clinical efficacy between the two groups [n (%), N = 45]

Group	Significantly effective	Effective	Ineffective	Total effective rate	Change in 6MWD (meters)
A	18（40.00）	24（53.33）	3（6.67）	93.33%（42/45）	38±5.6
B	13（28.89）	23（51.11）	9（20.00）	80.00%（36/45）	21±7.2
χ^2				4.406	3.829
P-value				0.036	0.011

Therapeutic efficacy

Group A had higher total treatment effectiveness and improved 6-minute walking distance than group B ($p < 0.05$; Table 2).

PSQI scores

As shown in Figure 1, there was no significant difference in PSQI scores of patients before treatment between the two groups ($p > 0.05$). The PSQI scores of group A before and after treatment were 16.34 ± 2.35 and 8.47 ± 1.86, respectively, while the PSQI scores of group B before and after treatment were 16.29 ± 2.3 and 12.54 ± 1.74, respectively. The PSQI scores of the patients were reduced after treatment with combination of bosentan and sildenafil, when compared with the group given conventional treatment only ($p < 0.05$).

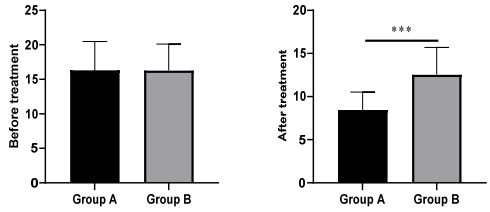

Figure 1: PSQI scores in the two groups before and after treatment. ***$P < 0.001$, comparison of PSQI scores of the two groups of patients after treatment

Cardiac functions

After treatment, the numbers of patients in group A with cardiac function classifications I, II, and III were 25 (55.56 %), 18 (40.00 %) and 2 (4.44 %), respectively. In group B, the number of patients with cardiac function classifications I, II, and III were 15 (33.33 %), 21 (46.67 %) and 9 (20.00 %), respectively. There were more level I patients, and fewer level III patients in group A than in group B ($p < 0.05$). These results are presented in Figure 2.

BDI scores

The BDI scores of patients in group A at T0, T1, T2, and T3 were 7.72 ± 0.54, 6.38 ± 0.34, 4.03 ± 0.47 and 2.56 ± 0.43, respectively. In group B patients, the BDI scores at T0, T1, T2, and T3 were 7.69 ± 0.52, 6.42 ± 0.39, 4.64 ± 0.51 and 3.14 ± 0.44 respectively. No significant differences in BDI scores at T0 and T1 between the two groups were obtained ($p > 0.05$). Group A had lower BDI scores at T2 and T3 than group B ($p < 0.05$). See Figure 3.

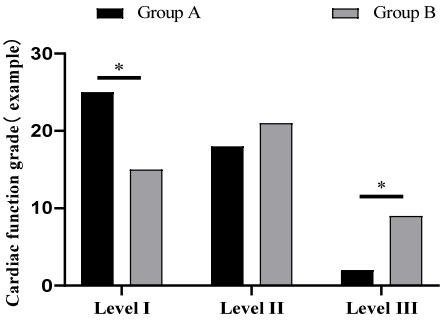

Figure 2: Comparison of the cardiac function in the two groups after treatment. Values are expressed as mean ± SD. *P <0.05

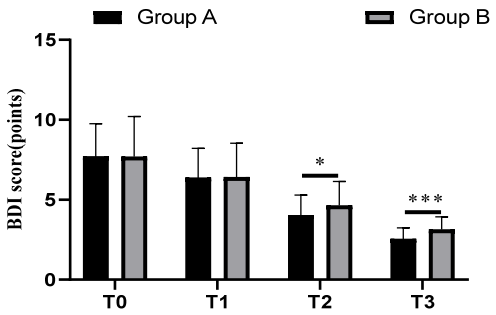

Figure 3: Comparison of BDI scores between the two groups of patients at different time points. *$P < 0.05$, ***$P < 0.001$

Cardiac output, cardiac index, and systemic arterial pressure

Two groups showed similar cardiac output, cardiac index, and systemic arterial pressure before treatment ($p > 0.05$). After treatment, there were markedly higher cardiac output and cardiac index, and a lower systemic arterial pressure in patients in group A than group B ($p < 0.05$; Table 3).

Table 3: Comparison of cardiac output, cardiac index, and systemic arterial pressure between the two groups before and after treatment (mean ± SD, n = 45)

Group	Cardiac output(L/min)		Cardiac index L/(min·m^2)		Systemic arterial pressure (mmHg)		Pulmonary arterial pressure	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
A	3.64±1.52	5.48±1.24	2.59±0.68	3.83±0.75	85.53±7.83	81.02±6.52	86.52±9.21	80.38±3.65
B	3.67±1.55	4.24±1.26	2.61±0.65	3.02±0.72	85.49±7.79	83.83±6.49	86.56±9.24	84.73±9.22
t	0.093	4.705	0.143	5.226	0.024	2.049	0.024	2.891
P-value	0.926	0.000	0.887	0.000	0.981	0.043	0.963	0.043

Table 4: Comparison of incidence of adverse reactions between the two groups of patients [n (%)]

Group	Urticaria	Tachycardia	Hypoglycemia	Total incidence
A	1（2.22）	0（0.00）	1（2.22）	4.44%（2/45）
B	2（4.44）	3（6.67）	3（6.67）	17.78%（8/45）
χ^2				4.050
P-value				0.044

Incidence of adverse reactions

Table 4 shows that post-treatment adverse reactions were significantly lower in group A patients than in group B ($p < 0.05$). Early-mid-term follow-up study 12 months after treatment showed that 43 patients did not complete the study: 20 patients died (7 in group A, and 13 in group B), while 23 patients discontinued.

DISCUSSION

Some scholars believe that PH is a common complication of congenital heart disease [10]. In clinical practice, PH is characterized by progressive failure of right heart function and progressive increase in pulmonary vascular resistance. Thus, PH is a primary cause of death in congenital heart disease cases. It results from increased pulmonary arterial resistance due to the fact that the patient's pulmonary blood vessels are in a state of high pressure and high blood flow. The disease causes the intima of the pulmonary arterioles to be impacted by abnormally increased shear forces which damage endothelial cells. The interaction of cytokines reduces cell apoptosis but invigorates cell proliferation. This thickens the intima of pulmonary arterioles and accumulates extracellular matrix. These pathological processes result in irreversible changes in the pulmonary vascular system [11,12].

Sildenafil is a selective phosphodiesterase inhibitor which increases the concentration of cyclic guanosine monophosphate (cGMP) in pulmonary vascular cells and promotes the production of endogenous nitric oxide (NO), leading to relaxation of pulmonary blood vessels. At the same time, the drug is effective in inhibiting anti-platelet and vascular proliferation [13]. Bosentan, an oral endothelin receptor antagonist, is a drug highly recommended in the European pulmonary hypertension diagnosis and treatment guidelines. On administration, bosentan blocks ETA and the binding of ET to receptors, and exerts anti-fibrotic, anti-inflammatory, and anti-proliferative effects [14].

Cardiac function classification is a method used for clinical evaluation of the degree of impairment of cardiac function in patients. It basically reflects the severity of the disease, and is of great value for selection of treatment options for patients, as well as evaluation of labor capacity and the prognosis of the disease [15]. In this study, the group treated with bosentan-sildenafil combination had more level I patients (25 vs 15) and fewer level III patients (2 vs 9) than the group given conventional treatment. This shows that combination of the two drugs succeeded in enhancing the heart function of patients with severe PH by reducing the clinical symptoms and improving prognosis of the disease. In addition, it was confirmed in this study that group A patients who received the combination treatment exhibited a lower incidence of adverse reactions after treatment than group B patients. This finding conform to the results of Meng *et al* [16].

CONCLUSION

The results obtained in this study have demonstrated that the combination of bosentan and sildenafil improves the sleep quality and cardiac functions of patients with severe PH, and mitigates the associated clinical symptoms. The combined treatment is highly safe and curative.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Zhe Cui and Lin Geng designed the study and collected the data. Zhe Cui analyzed the data and wrote the manuscript. Zhe Cui and Lin Geng revised the manuscript.

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