International Journal of Medical Science and Clinical Inventions 4(5): 2888-2893, 2017
DOI:10.18535/ijmsci/v4i5.03 **ICV 2015: 52.82**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article

To Study the Role of Bosentan in Patients with Irreversible Obstructive Pulmonary Disease Having Mild to Moderate Pulmonary Arterial Hypertension

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ABSTRACT:

Aim: To determine the efficacy of the drug Bosentan, an endothelial receptor antagonist, in patients of secondary pulmonary arterial hypertension having irreversible obstructive pulmonary disease on the basis of improvement in 6 minutes walk test (6MWT) and reduction in Pulmonary Arterial Systolic Pressure (PASP) measured by echocardiography.

Methods: This prospective clinical study was conducted over a period of 18 months from October 2015 to March 2017. Patients attending OPD or admitted in the Respiratory Medicine ward with irreversible obstructive pulmonary disease and associated mild to moderate PAH (PASP 25-55 mm of Hg), confirmed by echocardiography, were enrolled. These patients were administered an oral dose of Bosentan 62.5mg twice a day for 4 weeks followed by dose increment to 125 mg twice a day for a duration of 8 weeks. Baseline and 12 weeks values of PASP, 6MWT, SPO_2 and spiromateric data were compared.

Results: Treatment with Bosentan for 12 weeks in patients with PAH secondary to irreversible obstructive airway disease resulted in a significant improvement in primary end points. PH decreased from 47.54 ± 6.15 mm Hg to 39.19 + 6.17 mm Hg and 6MWD increased from 320.71+52.97 metres to 410+55.74 metres with a mean improvement of 89.29+ 31.78 metres. However, secondary measures of efficacy including oxygen saturation and lung function parameters (FEV1/FVC, FEV1 and FVC) did not show any significant improvement.

Conclusion: Bosentan appears to have a significant clinical benefit in patients with PAH secondary to irreversible obstructive pulmonary disease with significant improvement in the 6 MWD and PASP.

Key Words: Pulmonary arterial hypertension; 6 minute walk distance; Pulmonary arterial systolic pressure; Pulmonary function test; Echocardiography

INTRODUCTION:

Pulmonary arterial hypertension (PAH) is a multi-factorial, progressive disease with substantial mortality and morbidity. Defined as a sustained elevation in mean pulmonary arterial pressure of >25 mm of Hg at rest in the absence of raised left sided cardiac pressure[1], American Thoracic Society categorized PAH into Mild PAH (PASP 25-40 mmHg), Moderate PAH (PASP 41-55 mmHg) and Severe PAH (PASP >55 mmHg)[2].

In the recent classification pulmonary hypertension secondary to irreversible obstructive pulmonary disease is listed in a subgroup of diseases associated with hypoxemia and/or lung disease[3]. Pulmonary functional abnormalities cause gas exchange abnormalities and chronic hypoxia resulting in pulmonary vasoconstriction and leading to Pulmonary Arterial Hypertension[4].

The exact process that initiates the pathological changes seen in pulmonary arterial hypertension is still unknown even though it is recognized that pulmonary arterial hypertension has a multi-factorial pathobiology. The increase in pulmonary vascular resistance may also be related to the endothelial dysfunction.

As PAH progresses, vascular remodelling occurs, characterized by a proliferative and anti-apoptotic state of cells within the vascular wall (smooth-muscle cells, fibroblasts and endothelial cells) resembling neoplasia[5-7]. Clones of endothelial cells proliferate and give rise to plexiform lesions, the pathologic hallmark of this condition, while smooth muscle cells and myofibroblasts proliferate and lead to medial hypertrophy and adventitial hyperplasia. [5-8]

Disruption of the extracellular matrix with elastase activation, infiltration of inflammatory cells and thrombosis in situ combine to reduce the cross-sectional area of the small pulmonary arteries and stiffen the large pulmonary arteries, thus increasing the right ventricular afterload and leading to right heart failure.[5]

Bosentan, an endothelin receptor antagonist, is a neuro-hormone the effects of which are mediated by binding to ETA and ETB receptors in the endothelium and vascular smooth muscle with a slightly higher affinity for ETA receptors. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. The clinical impact of

dual endothelin blockage is unknown.[9]

Since a few epidemiological studies have been carried out in our country to study the safety and efficacy of Bosentan in secondary PAH, the present study was conducted to investigate whether or not Bosentan, a dual antagonist of endothelin receptors, is able to improve clinical, functional and haemodynamic status in patients of irreversible obstructive pulmonary disease with associated pulmonary hypertension.

MATERIAL AND METHODS:

Subjects and Sampling:

It was a prospective clinical study conducted in the Department of Respiratory Medicine of Subharti Medical College, Meerut from October 2015 to March 2017. The study was initiated after receiving clearance from the Ethical Committee of the hospital and an informed consent was taken from all the patients enrolled.

Inclusion criteria:

1. Patients aged >18 years.
2. History and examination suggestive of irreversible pulmonary lung disease in compliance with chest radiographic and spirometry findings.
3. With or without past history of tuberculosis with associated Pulmonary Arterial Hypertension detected by Echocardiography.
4. Based on echocardiography, a PASP value between 25 mm Hg and 55 mm Hg.

Exclusion criteria:

1. Patient falling in WHO functional class IV.
2. Pulmonary arterial hypertension above 55 mm Hg.
3. Resting hypotension or systolic B.P < 90 mmHg in supine position.
4. Having suffered from acute myocardial infarction, stroke or life threatening arrhythmias within last 3 months.
5. Known hypersensitivity to endothelin receptor antagonist.
6. Requiring or had received Cyclosporine A or Glibenclamide within 1 month of enrolment.
7. Severe renal impairment with creatinine clearance <30ml/min or deranged liver function tests.
8. Pregnancy.

Before prescribing the treatment, all subjects were evaluated for basic laboratory investigations including Complete blood count, Liver function test, Kidney function test, Random blood sugar, Peripheral saturation by pulse oximetry, ECG, Chest radiograph (PA view), Pulmonary function test, Immuno-compromised status assessment, 2D-Echo & 6-MWT as per the American Thoracic Society (ATS) guidelines. Patients were also classified according to WHO functional class assessment for pulmonary arterial hypertension.

In order to avoid inter observer variations, echocardiography of all patients enrolled in the study was performed by a common observer. Similarly, 6 MWT of all enrolled patients was performed by a common observer.

To all patients in study group, Bosentan was prescribed in oral form in the dosing of 62.5 mg twice daily for the first 2 weeks. It was followed by a dose increment to the target dose of 125 mg twice daily for the next 8 weeks.

Outcome measurements:

Patients were assessed after 24 hours and at 12 weeks of treatment and on as and when required basis. The primary end-point were exercise capacity at week 12 (measured by the 6-MWT) and PASP (measured by 2-D ECHO). Secondary measures of efficacy included: oxygen saturation by pulse oximetry and lung function parameters such as FEV1/FVC, FEV1 and FVC based on spirometry. Safety of drug was appraised by the number of adverse events and laboratory assessment.

Data Analysis:

The data accumulated was analyzed using SPSS version 20. Continuous variables were expressed in terms of mean ± SD. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables within the group at baseline and 12 weeks was performed using paired t test. Association between variables was considered statistically significant if p-value was < 0.05.

RESULTS:

75 patients with irreversible obstructive pulmonary disease with associated mild to moderate PAH were enrolled in the study. However, at the end of study period only 42 patients were included in the analysis of study results. 33 patients were excluded as they were either lost to follow up or refused to take treatment and be part of the study group.

The mean age of the patients enrolled in our study was found to be 54.28 + 8.93 years. Majority of the patients (n=34; 80.94%) were in the age group of 48-68 years followed by 6 patients (14.28%) in the age group of 38-48 years and 2 patients (4.7%) in the 28-38 year age group. No patient was found in the age group of 18-28 years. Among the 42 patients enrolled in study, male to female ratio was found to be almost equivalent (11:10) with 22 (52.38%) males and 20 (47.61%) females [Table 1].

Table 1: Age and Gender wise distribution of patients in the study group

Age Group	No. of Patients (n=42)	Percentage (%)
18-28	0	0.00%
28-38	2	4.7%
38-48	6	14.28%
48-58	17	40.47%
58-68	17	40.47%
Gender wise distribution		
Male	22	52.38%
Female	20	47.61%

Table 1 shows age and gender wise distribution of patients in the study group.

History of present or past history of smoking was positive in 33 patients (78.6%) while, 9 patients (21.42%) were lifetime non-smokers [Table 2].

Table 2: Distribution according to Smoking history and previous history of tuberculosis

Age Group	No. of Patients	Percentage (%)
Distribution according to Smoking history		
Smokers	33	78.57%
Non-smokers	9	21.42%
Distribution according to previous history of tuberculosis		
T.B HISTORY		
Yes	7	16.66%
No	35	83.33%

History of past tuberculosis was present in only 7 patients (16.66%). Spirometry results showed that majority of patients (n=40, 95.23%) had obstructive pattern while 2 (4.76%) patients had mixed obstructive and restrictive anomaly.

Evaluation of patients on the basis of symptoms revealed that dyspnoea was the most common presenting symptom being present in all the patients (100%). The second most common symptom was cough being present in 29 patients (69.04%) while fatigue was present in 20 patients (47.61%) and chest pain in 12 patients (28.57%). None of the patients had complaint of syncope [Table 3].

Table 3 : Distribution according to Clinical features

SYMPTOMS	No. of Patients out of enrolled cases	Percentage (%)
Dyspnoea	42	100.00%
Cough	29	69.04%
Fatigue	20	47.61%
Chest Pain	12	28.57%
Syncope	0	-

Majority of the patients were symptomatic for a long period of time with 21 patients (n=50%) being symptomatic since last 5-10 years and 10 patients (n=23.8%) having symptoms longer than 10 years [Table 4].

Table 4: Distribution of patients according to the duration of illness, diagnosis and WHO functional class assessment of pulmonary hypertension

Duration	No. of Patients (n=42)	Percentage (%)
Distribution of patients according to the duration of illness		
0-5 yrs	7	16.66 %
5-10 yrs	21	50.00 %
10-15 yrs	10	23.80 %
15-20 yrs	4	09.52 %
Diagnosis wise distribution of the patients		
COPD	35	83.33%
Post T.B OAD	7	16.66%
Distribution based on WHO functional class assessment of pulmonary hypertension		
II	17	40.47 %
III	25	59.52 %

Table 4 shows distribution of patients according to the duration of illness, diagnosis and WHO functional class assessment of pulmonary hypertension

Based on WHO functional class assessment of pulmonary hypertension, 25 patients out of 42 (59.5%) belonged to class III and 17 (40.47%) to class II.

Electrocardiogram (ECG) was found to be normal in 14 (33.33%) patients. However, ECG was suggestive of right atrial enlargement (n=17, 40.5%), right axis deviation (n=14, 33.3%) and right ventricular hypertrophy (n=8, 19%) in patients enrolled in our study [Table 5].

Table 5: Distribution of patients according to ECG findings

ECG FINDINGS	**No. of Patients**	**Percentage (%)**
Right Axis Deviation	14	33.33%
Right Atrial Enlargement	17	40.47%
Right Ventricular Hypertrophy	8	19.04%
Normal	14	33.33%

Evaluation of chest radiograph of the enrolled patients revealed emphysema and fibrosis in 25 (59%) & 7 (16.66%) patients respectively. Prominent broncho-vascular markings on chest radiograph were seen in chest radiography of 10 (23.80%) patients.

Results of 6 minute walk test were compared between pre and post therapy with Bosentan in the recommended dosing. The distance walked by each patient during 6-MWT revealed significant improvement ($p<0.05$) between pre and post drug period. The mean distance walked by patients at baseline was 320.71 ± 52.97 metres and 410 ± 55.74 metres at 12 weeks with an improvement of 89.29 ± 31.78 metres following therapy.

As with the 6- MWT results, Bosentan was found to be effective in reducing the PASP in irreversible obstructive disease associated PAH. PASP measured by 2-D ECHO at baseline was 47.54 ± 6.15 mm Hg and at 12 weeks was 39.19 ± 6.17 mm Hg with a statistically significant ($p<0.05$) improvement by a decrease of PASP by 8.35+4.59 mmHg after a 12 weeks therapy with Bosentan. [Table 6]

Table no 6 :

S. No.	Characteristics		Mean + S.D.		P value
			At Baseline	After 12weeks	
1.	SPo2		93.83 ± 1.41	94.23 ± 1.20	P > 0.05
2.	PFT	FEV1/FVC	57.52 ± 9.45	56.21 ± 8.10	P > 0.05
		FEV1	49.04 ± 9.47	45.69 ± 8.20	P > 0.05
		FVC	88.04 ± 6.35	87.92 ± 6.37	P > 0.05
3.	6 MWT		320.71 ± 52.971	410 ± 55.743	P < 0.05
4.	PASP – ECHO		47.548 ± 6.153	39.119 ± 6.173	P < 0.05

*$p < 0.05$ shows a significant difference at 5% level of significance

The above table depicts a significant difference ($p < 0.05$) at 5% level of significance in 6MWT and PASP.

Measurement of SPO_2 values of all patients at baseline and at 12 wks by pulse oximetry revealed no significant improvement in SPO_2 in pre and post drug period. The mean SPO_2 at baseline was 93.83% and was 94.24% after 12 wks. Though, the absolute value of oxygen saturation improved, the difference between mean of pre and post study period was insignificant statistically ($p>0.05$).

DISCUSSION:

In developing country like India where poverty is wide

spread, affordability to get Right Heart Catheterization (RHC) for the diagnosis of PAH which is costly and available only at specialized centres, is a major problem. In a city like Meerut where the present study was conducted has a roughly estimated population of 3.4 million[10] with none of the centres having the facility for RHC available. Right Heart Catheterization, pulmonary vasoreactivity testing and pulmonary angiography are established diagnostic tools in patients with PAH, but these can be performed in experienced centres only and are also associated with complications such as related to venous access (e.g.,hematoma, pneumothorax), arrhythmias and hypotensive episodes related to vagal reactions on pulmonary vasoreactivity testing.[11]

This is also supported by the study results of Homma A et al[12] who concluded that in patients with PAH awaiting transplant, PASP estimation by echocardiogram do correspond but do not serve as an absolute accurate predictive model of PASP as measured by Right Heart Catheterization.

Selimovic N et al[13] in a study of 42 patients concluded that Doppler echocardiography can be used for adequate estimation of Periperal Vascular Resistanse in patients with PAH and may reduce the need for invasive follow-up in these patients.

In a prospective study by Khouli H et al[14] to evaluate the hemodynamic comparison between RHC and transthoracic Echocardiography in 56 critically ill patients, they found transthoracic echocardiography (TTE) to be a useful diagnostic tool in determining the etiology of cardiopulmonary compromise when initial clinical assessment is limited. TTE was highly suggestive of Pumonary Embolism and Cardiac Tamponade in 3 patients where RHC was not. While both methods can be complementary to each other, bedside transthoracic echocardiography is an acceptable non-invasive alternative to right heart catheterization in determining the etiology of cardiopulmonary compromise in most critically ill patients when initial clinical assessment is limited. So, in our study we sought to diagnose secondary PAH on the basis of Echocardiographic findings followed by Clinical assessment of these patients. The mean age of patients in our study was 54.28 ± 8.93 years and male to female ratio was 11:10 with almost equal number of males and females. Similar studies for assessment of PAH in COPD patients as done by Stolz D et al[15] (69.5 ± 8.8 years) and Valerio G et al[16] (966 ± 9 years) also revealed the same pattern with advanced age. In another study conducted by King T et al[17] in patients of Idiopathic Pulmonary Fibrosis, the mean age was 63.8 ± 8.4 years.

This can be explained due to late presentation of lung disease patient to outpatient department and symptoms of PAH being similar to lung disease.

Regarding gender distribution, similar trend was seen in studies done by Stolz D et al[15] and Valerio G et al[16] with M:F ratio 11:9 and 13:3 respectively. King T et al[17] in 2011 also showed similar results with M:F ratio 296:111.

In the present study 33 patients out of 42 patients had history of smoking. Another study conducted by Stolz D et al[15] showed similar trend with 18 out of 20 patients being ex smokers. This can be explained by the fact that smokers are more likely to develop Chronic Obstructive Airway Disease. Smoking causes chronic airway inflammation which leads to structural damage, remodelling of the airways and impaired mucocilliary clearance.

PAH is thought to be caused by oxidative vascular damage by reactive nitrogen species produced by cigarette smoke. eNOS is also suggested to be responsible for vascular oxidative damage in cigarette smokers. Although role in human models is uncertain.[18]

In the present study 7 out of 42 patients had history of tuberculosis. Similar results were shown in a study done by Ahmed A et al[19] in 14 treated Pulmonary Tuberculosis cases. This is due to the fact that treated Pulmonary Tuberculosis results in residual structural damage and Pulmonary functional abnormalities leading to gas exchange abnormalities and chronic hypoxia. Chronic hypoxia causes pulmonary vasoconstriction which results in Pulmonary Arterial Hypertension. In the present study most common symptom was dyspnoea which was present in all patients enrolled followed by cough (69.04%), fatigue (47.61%) and chest pain (28.57%). In a study conducted by Stolz D et al[15] showed that maximum number of patients presented with symptoms of dizziness and peripheral edema. The first symptom that patients with PAH present, is dyspnoea. Other symptoms that patients may present with are fatigue, chest pain, syncope and peripheral edema. All the patients in our study had presented with established PAH symptoms.

In our study the duration of illness between 5-10 years had maximum number of patients which was significant clinically with diagnosis. Study done by King TE et al[17] in patients of IPF showed median of symptoms as 2 years with range (0.11-13.3). This is because the patients with chronic lung disease have mild symptoms in the early stage and progresses gradually with time to which patients initially do not pay much attention and usually depend on basic treatment. This could also be explained as most of the patients first come in contact with local doctors instead of specialist.

Majority of patients in our study i.e. 35 out of 42 patients, the cause for their secondary PAH came out to be COPD. A study done by Valerio G et al[16] and Stolz D et al[15] in patients with COPD and severe COPD respectively having PAH supports our study. As COPD is prevalent in our country it could be the probable explanation of COPD being the most common cause in cases of secondary PAH presenting to us.

The Functional Classification system of the NYHA has been adopted by the WHO for use in classifying symptoms in patients with PAH. In our study 2/3rd (25/42) of the patients belong to class III and rest 1/3rd (17/42) to class II according to this classification. Ratio was similar to that of patients enrolled in study by Humbert M et al[20] with 17 patients in class III and 5 patients in class II. Similarly studies by Kemp K et al[21], Rubin J et al[22] and Joglekar M et al[23] on patients with secondary PAH had more patients in class III as compared to class II.

The rate of PH progression in COPD is normally slow. The presence of PH is a strong predictor of mortality in COPD. The prevalence of PH in COPD depends on the severity of the disease and degree of lung parenchymal abnormalities. The underlying parenchymal remodelling process with accompanying hypoxia causes some natural loss of overall vascular cross-sectional area and thus an increase in peripheral vascular resistance.

There is a great interest in knowing whether new specific PAH therapy could also be beneficial in more prevalent forms of PAH, such as that associated with irreversible pulmonary disease. In our study, PASP decreased from a mean value of 47.54 ± 5.06 mmHg at baseline to 39.11 ± 6.17 mmHg after a 12 weeks administration of Bosentan with a mean decrease of 8.4 ± 4.6 mmHg which was found to be statistically significant($p<0.05$). Sitbon O et al[24] showed similar results in patients of primary PAH or associated with scleroderma. Similar results were shown in study conducted by Onda N et al[25] investigating the effect of Bosentan on hemodynamic parameters in one patient with pulmonary hypertension secondary to idiopathic pulmonary fibrosis in contrast to studies done by Stolz D et al[15] and Joglekar A et al[23] as they found no significant improvement in PASP after 3 months of Bosentan therapy in 20 COPD patients and patients of systemic sclerosis respectively.

Bosentan may help all Irreversible pulmonary Disease patients, even those not diagnosed with PAH. In the study, there was a significant improvement in results of 6 MWT from 320.71 ± 52.97 metres at baseline to a mean of 410 ± 55.74 metres at 12 weeks with an improvement of 89.28 ± 29.25 metres which is statistically significant ($p<0.05$). A controlled clinical trial with the largest number of patients (BREATHE-1) study by Rubin LJ et al[26] in which 213 patients with secondary PAH were enrolled and the mean 6-MWD increased by 36 m as compared to the placebo group which supports our findings. Similar trend was also shown by studies done by Sitbon O et al[24] and Valerio G et al[16] with a significant improvement in 6MWD.

CONCLUSION:

Our study to determine the safety and efficacy of Bosentan (endothelin receptor antagonist) in patients of Irreversible Obstructive Pulmonary Disease with mild to moderate PAH having followed up for a duration of 12 weeks concluded that bosentan is safe and effective for the treatment of secondary PAH as there was statistically significant improvement in the values of 6 MWT and PASP after administration of the drug following 12 weeks duration. The drug has good safety profile in patients with secondary PAH at this dosage as there were no major side effects seen during the study.

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