Original Article

Investigating The Effects Of Tadalafil And Bosentan On The Pulmonary Arterial Hypertension, Cardiac Output And Prognosis Of Mechanical Ventilation In Chronic Obstructive Pulmonary Disease Patients Under Mechanical Ventilation

[1]Mohammad Reza Ghaffary, [2*]Shamsi Ghaffary

[1]Associate Professor of Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, Email: Mohammadrezaghaffary@gmail.com
[2*]Associate Professor of Pediatric Cardiology, Medical Faculty, Tabriz University, Tabriz, Iran, Email: Shamsi.ghaffari@gmail.com
DOI: 10.47750/pnr.2022.13.04.261

Abstract

Introduction: The desirable effects of such medications as Tadalafil and Bosentan on the right heart hemodynamics to treat the pulmonary hypertension of the patients with the exacerbation of chronic obstructive pulmonary disease under mechanical ventilation principally increase the cardiac output by increasing the left ventricular preload, as the effects of this increase are statistically valuable in improving the prognosis of the patients. For this, the present study investigates the non-invasive effects of these therapeutic agents (tadalafil and bosentan) on the pulmonary hypertension of the patients with the chronic obstructive pulmonary disease (COPD) who are under the mechanical ventilation.

Procedure: This study was a randomized clinical trial that was carried out at the Imam Reza Hospital (Tabriz University of Medical Sciences, Iran) from 2018 to 2019, with the participation of 200 patients diagnosed with COPD and pulmonary arterial hypertension. Having been randomly assigned to two groups, the bosentan group received a 125 mg bosentan medication twice per day, while the tadalafil group received 40 mg tadalafil once per day, as before and after the intervention, stroke volume, left ventricle output and pulmonary arterial hypertension were measured and compared. Descriptive and inferential statistics were used for the comparison of the two groups, as the P level of less than 0.05 was significant.

Results: Results indicated the significant effects of both drugs on reducing the pulmonary arterial hypertension, though the post-intervention inter-group comparison suggested no significant statistical difference between the two groups. On the other hand, both drugs created significant improvements of FEV1, PaO2 and PaCO2. However no significant difference was noted between the two groups in terms of the duration of the mechanical ventilation and the number of patients being successfully removed from ventilators.

Conclusion: Tadalafil and bosentan were found to improve the oxygenation level, reduce pulmonary arterial hypertension and reduce the time needed for assisted ventilation.

Keywords: Tadalafil, Bosentan, COPD, Pulmonary arterial hypertension.

INTRODUCTION

Chronic obstructive pulmonary diseases are among the top four causes of mortality across the world, which are projected to make up the top three causes of mortality by 2020. In patients with this disease, the clinical diagnosis of Cor Pulmonale is regarded a negative prognosis. Hemodynamic examinations of these patients have indicated that an increase of 10 mm mercury in the pulmonary arterial hypertension will increase mortality rates by four times (1). Today, Oesophageal Doppler Monitor (ODM) is widely used to examine the cardiac output and volume of intravascular fluids in ICUs. This monitoring method uses a small ultrasound probe in the esophagus through the mouth or nose. This probe generates low-frequency (4 MHZ) ultrasound waves near the aorta which reflect after colliding with the red blood cells moving down the body (2). Using the doppler monitoring, the returned signals can be used to determine the rate of blood circulation. Then, approved nomograms are used to determine

volume data such as stroke volume or cardiac output. Various studies that were conducted since 2000 referred to this technique as a selective non-invasive technique in ICUs (3).

This research used the OCM technique in COPD patients with pulmonary hypertension under mechanical ventilation to investigate the effects of tadalafil and bosentan drugs on the stroke volume and cardiac output of the left ventricle, and finally the outcome of the mechanical ventilation. Increased preload in the presence of certain contraction and afterload will increase stroke volume. In the presence of certain systemic resistance, the blood circulation rate in the aorta depends on the contractility of the left ventricle, and could create peak doppler waves in the ODM. Since the peak blood circulation in the aorta occurs in the first few thousandths of seconds of the aortic valve opening, but systemic resistance increases during the systole, it is thus concluded that the ODM is not, in fact, a function of the systemic resistance, and is mostly determined by the contraction and preload (4).

A clinical study by Castellvi et al. (2020) investigated the effects of Bosentan on the pulmonary arterial hypertension. They concluded that the prescription of bosentan could control the pulmonary arterial hypertension and, consequently, reduce mortality rates. They also suggested that more researches with higher sample volumes were warranted (5).

Another clinical study conducted by Safdar et al. (2017) compared Macitentan and Bosentan in patients with pulmonary arterial hypertension. In this study, they measured the variable of pulmonary arterial hypertension of the two groups after the intervention, and concluded that the pulmonary artery in the bosentan group had significantly reduced compared to the Macitentan group. In the end, the researchers considered the use of bosentan to be useful to treat pulmonary arterial hypertension, suggesting that this medication be added to the drug regimen of the patients (6).

Another study by Barst et al. (2011) aimed to investigate the addition of tadalafil to the bosentan drug regimen in patients with pulmonary arterial hypertension. In this clinical study, 405 patients were randomly divided into two groups. For one group, only bosentan was prescribed, while for the other group, tadalafil, along with bosentan was prescribed. The level of pulmonary arterial hypertension of the two groups was examined after 16 weeks, and it was determined that the addition of tadalafil to the bosentan drug regimen could leave highly desirable effects on reducing pulmonary arterial hypertension. In the end, they proposed to use this drug along with bosentan (7).

Currently, there is no screening test for the pulmonary hypertension in the COPD patients, as recent reports of using NT-pro-BNP to diagnose pulmonary arterial hypertension during the exacerbation of the disease lacked sufficient specificity. Thus, for the pulmonary hypertension, the right heart catheterization is the only definitive diagnostic test which can evaluate the increased severity of pulmonary arterial hypertension (8). In the acute exacerbation of COPD, the right heart suffers failure which increases the end-diastolic pressure and volume, thus causing peripheral edema, along with congestion. This may not be associated with increased pulmonary hypertension which indicates the effects of unknown medications on the contraction of the left ventricle (9,10).

The role of phosphodiesterase inhibitors to treat pulmonary vascular hypertension has attracted the attention of researchers over the past years. On the other hand, these inhibitors play the role of the Antiproliferatives. All three inhibitors (Sildenafil, Tadalafil and Vardenafil) cause considerable pulmonary vascular vasodilatation, if maximum dosages are administered (11). Tadalafil is a selective phosphodiesterase with long-lasting effects demonstrated in various studies, such as clinical sign improvement, activity tolerance ability, improved hemodynamic and delayed progression of disease trend. Small-volume studies on COPD patients with pulmonary hypertension have demonstrated that Sildenafil acutely improves hemodynamics, but this improved hemodynamics is associated with worsening hypoxemia. Disregard of the fact that the studies were limited and could not be referred to, they were mainly aimed at COPD patients in the PAH Group I (12).

The effects of hypovolemia in ODM are characterized by the thinning of the peak flow base, along with the normality of the peak rate. For this, the reduction or increase of the preload of the left ventricle can be easily determined from the analysis of the peak flow curve of the ODM. The present study hypothesizes that the effects of such medications as tadalafil and bosentan, if found desirable, on the right heart hemodynamics to treat the pulmonary hypertension of the patients with the exacerbation of chronic obstructive pulmonary disease under mechanical ventilation will, in principle, increase the cardiac output by increasing the preload of the left ventricle, as the effects of this increase are statistically valuable in improving the prognosis of the patients (13,14). For this, the present study investigates the non-invasive effects of these therapeutic agents (tadalafil and bosentan) on the pulmonary hypertension of the patients with the chronic obstructive pulmonary disease (COPD) who are under the mechanical ventilation.

Research Method

This is a clinical trial study which investigates patients with pulmonary arterial hypertension. A total of 200 people with the disease were examined in this study. The research population consisted of patients with pulmonary arterial hypertension, admitted to the Imam Reza Hospital, affiliated with the Tabriz University of Medical Sciences. Sampling in this method was made via convenience methods and the patients in the lung-specific ICUs entered the study. A review of the similar studies and pilot studies led to the selection of a final volume of 200 people, assigned to two 100-peole groups.

Inclusion criteria were ages higher than 18, history of COPD development under treatment, hospitalization in pulmonary ICUs, being under controlled respiration or connected with a ventilator, average rate of pulmonary arterial hypertension of over 25 mm mercury, pulmonary vascular resistance of over 3, minimum age of 40 kg, placement in the II and III class in accordance with the World Health Organization in terms of PAH, and PAP of over 25 mm mercury.

Having entered the study, the patients were divided into two groups of 1) bosentan and 2) tadalafil using random number table. The randomized list was made by assigning Codes B and T to the bosentan group (two tablets a day) and tadalafil group (one tablet a day).

The patients were treated with the drugs for a week, with the bosentan group receiving 125 mg twice a day (tablet made by Tehran's Faran Shimi Co.), and the tadalafil group receiving 40 mg once a day (tablet made by Tehran's Loghman Co.). Both drugs were in tablet forms which were prescribed by one single physician. After the ending of the therapeutic term which lasted for seven days for each group, the patients had their stroke volume, left ventricular output and pulmonary arterial hypertension measured. In the end, prognosis of the mechanical ventilation was compared based on the duration of the mechanical ventilation and successful and unsuccessful ventilator separation.

All the data were analyzed by the SPSS (version 20).

Findings

The standard deviation and mean age of the subjects in the study were 63.5±49.85 years, respectively; out of the total subjects, 112 ones were women. Also, the standard deviation and average body mass of the subjects were 25.14±61.2, respectively. No statistical difference was noted between the aforementioned variables between the two groups.

A review of echocardiography results suggested that in the beginning of the intervention, the standard deviation and mean pulmonary arterial hypertension were 6.21±49.13 mm mercury, respectively; also, the standard deviation and mean FEV1, PaO2 and PaCO2 were 5.81±38.29, 7.11±53.45 and 6.03±51.59, respectively, suggesting no statistically significant difference between the groups.

An intra-group comparison of the pulmonary arterial hypertension at the end of the study suggested that both drugs had significantly reduced the pulmonary arterial hypertension; however, the post-intervention inter-group comparison suggested that no statistical difference was noted between the two groups. Pulmonary arterial hypertension results before and after the intervention are given in Table 1.

Table 1: Intra- and inter-group comparison of the pulmonary arterial hypertension before and after the intervention

Variable	**Studied groups**		**P Value**
	Group B (N=100)	**Group T (N=100)**	
Before the intervention	48.95 ±6.15	49.49 ±6.41	0.221
After the intervention	23.19 ±2.29	21.49 ±2.78	0.248
P Value	0.009	0.005	-

The intra-group comparison of the FEV1 in the end of the study suggested that both drugs had significantly increased FEV1; however, the post-intervention inter-group comparison suggested that no statistically significant difference was noted between the two groups. Table 2 presents the FEV1 results before and after the intervention.

Table 2: Intra- and inter-group comparison of FEV1 before and after the intervention

Variable	**Studied groups**		**P Value**
	Group B (N=100)	**Group T (N=100)**	
Before the intervention	39.01±5.29	38.15±5.29	0.119

After the intervention	45.18±6.19	46.11±6.18	0.159
P Value	0.029	0.019	-

The intra-group comparison of the PaO2 in the end of the study suggested that both drugs had significantly reduced PaO2; however, the post-intervention inter-group comparison suggested that no statistically significant difference was noted between the two groups. Table 3 presents the PaO2 results before and after the intervention.

Table 2: Intra- and inter-group comparison of PaO2 before and after the intervention

Variable	**Studied groups**		P Value
	Group B (N=100)	**Group T (N=100)**	
Before the variable	51.99±6.99	51.14±6.09	0.214
After the variable	44.05±5.21	43.91±5.89	0.225
P Value	0.018	0.011	-

The intra-group comparison of the PaCO2 in the end of the study suggested that both drugs had no significant effect on increasing the PaCO2; however, the post-intervention inter-group comparison suggested that no statistically significant difference was noted between the two groups. Table 4 presents the PaCO2 results before and after the intervention.

Table 2: Intra- and inter-group comparison of PaCO2 before and after the intervention

Variable	**Studied groups**		P Value
	Group B (N=100)	**Group T (N=100)**	
Before the variable	51.89±6.14	51.89±6.19	0/297
After the variable	51.78±5.89	52.02±5.49	0/359
P Value	0.089	0.081	-

A comparison of the duration of mechanical ventilation and the number of successful removals of ventilation suggested that the duration of the mechanical ventilation in the tadalafil group had significantly decreased compared to the bosentan group; on the other hand, the number of patients being removed from ventilator in the tadalafil was insignificantly fewer than those of the bosentan group. The comparison of the mechanical ventilation and removal from ventilator are given in Table 5.

Table 5: Comparison of duration of mechanical ventilation and removal from ventilators in the studied patients

Variable	**Studied groups**		**P Value**
	Group B (N=100)	**Group T (N=100)**	
Duration of mechanical ventilation (day)	5.21±0.43	5.81±0.88	0.110
Removal from ventilators	59 people	63 people	0.089

Discussion

Pulmonary arterial hypertension (PAH) or progressive arteriopathy causes a heightened pulmonary arterial hypertension, which if, not treated, engenders in the failure of the right ventricle and finally increases mortality (15). Pathogenically, in this disease, there are several abnormalities with the endothelial system function which include dysfunctional prostacyclin and nitric oxide and sever reduction of endothelin. These abnormalities, if treated, will eventually help treat pulmonary arterial hypertension. These treatments include prostacyclin analogs, epoprostenol, treprostinil and iloprost (16).

Endothelin receptor antagonists (ERA), like bosentan serve as phosphodiesterase-5 inhibitors and has left positive effects with their short- and long-term effects. In fact, bosentan, along with the endothelin receptor antagonists, is

a derivative of prostacyclin which, if administered in a dual form, can treat pulmonary arterial hypertension. However, there are many patients who do not fully recover by these drugs; therefore, it is required to add some other drugs to their drug regimen (17).

In this connection, improved systemic and pulmonary hemodynamics in patients with HF and PH, who tolerate bosentan therapy, suggests that this treatment can be useful in at least half of the patients. Most importantly, the addition of bosentan to a standard HF treatment helps significantly reduce systemic hypertension and pulmonary resistance; thus, this therapy is useful in the treatment of the patients. This drug is a competitive and exclusive endothelin-1 receptor antagonist. This receptor increases in the patients with pulmonary arterial hypertension and seems to play a pathogenic role in this disease; since bosentan is the antagonist of this receptor, it may be useful to treat these patients (18).

The results of the present study are consistent with those of other studies by Rondelet et al. (2003) (19), MacLaughlin et al. (2006) (20), Maouchaers et al. (2010) (21), Kemp et al. (2012) (22) and Vis et al. (2013) (23).

Previous studies concluded that the addition of bosentan to the drug regimen to treat patients with pulmonary arterial hypertension helped improve their oxygenation; these were the results which support our study results. In the present study, bosentan was found to improve the patients' oxygenation, as PaO2 and PaCO2 saw improvements; meanwhile, ventilator-connected patients were extubated in a shorter time, and the need for the ventilator was alleviated (24).

In recent years, the use of phosphodiesterase-5 inhibitors has attracted attention, and in this connection, tadalafil is a drug that is prescribed for a single dose daily, which, compared to sildenafil, taken four times daily, is more popular in patients. Tadalafil inhibits the break-down of cGMP by phosphodiesterase to increase the cGMP level to prolong the relaxation of smooth muscles and enhance the blood circulation in the corpus cavernosum. The drug shows its effects within two hours.

The drug is well delivered into the tissues and binds to the plasma proteins by 97%. The drug metabolism is made by the hepatic P450 cytochrome (especially CYP3A4). The drug's half-life is around 17 hours. The tadalafil drug working to reduce the pulmonary hypertension relaxes the muscular cells of the wall of the blood vessels leading to the lungs, thus dilating blood vessels. This will, in turn, reduce hypertension in blood vasculature and cause the blood flow in the vessels to be easily made, which will, as a result, improve the functioning of the lungs and physical activities. Results of the preset study suggested that tadalafil could reduce pulmonary arterial hypertension. The results are also consistent with those of Takatsuki et al. (2012) (25), Henrie et al. (205) (26), Shiva et al. (2016) (27) and Hassoun et al. (2015) (28).

Production and release of NO are reduced following a dysfunctional endothelial. Reduction and unavailability of NO in the PAH could lead to reduced cGMP and increased pulmonary arterial vasoconstriction. PDE-5 is the predominant phosphodiesterase of the pulmonary vasculature which is responsible for the fast degradation and inactivation of cGMP. In the meantime, increased concentration of cGMP helps relax the smooth muscle of the pulmonary vasculature and dilate the pulmonary vascular substrate. Sildenafil and Tadalafil are the only PDE-5 inhibitors which are approved by the FDA.

Considering its effects, the tadalafil drug can help treat patients with pulmonary arterial hypertension. However, most previous studies have suggested that this drug cannot be effective in the full treatment of the patients, alone, and it should be prescribed in combination with other drugs such as sildenafil to leave its significant effects. Results of the previous studies and those of the present study are similar in that the drug alone cannot fully improve the patients. Also, the previous studies revealed that tadalafil can help improve the oxygenation of the patients with pulmonary arterial hypertension, as the present study results confirm it. Our study also demonstrated that the use of this drug can improve the pulmonary ventilation and oxygenation.

Conclusion

Tadalafil and Bosentan were found to improve oxygenation, reduce pulmonary arterial hypertension and reduce the duration of ventilation.

The limitations of this study are the short time allotted to examine the patients, low sample size, failure to examine the final results of the patients, and failure to examine the need for the assisted ventilation; thus, it is proposed to remove these limitations in future studies. Also, because none of the drugs could fully improve the patients, the two drugs are proposed to be prescribed together to determinate final status of the patients.

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