Research Brief

Effect of ivabradine on heart rate, functional capacity and pulmonary artery pressure in patients of COPD with cor pulmonale

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ABSTRACT

We studied the effects of heart rate reduction by ivabradine to the ongoing therapy in patients with chronic obstructive pulmonary disease (COPD) and cor pulmonale.100 patients of COPD with cor pulmonale with sinus heart rate $\geq$ 90 bpm were randomly assigned to either ivabradine 5 mg twice daily (50 patients) or placebo (50 patients) alongwith standard therapy. Assessment was done at baseline and after 6 months which included 6 min walk test (6MWT), dyspnea scoring by modified borg scale, Lung function test by forced expiratory volume in 1 s (FEV1) and pulmonary artery systolic pressure (PASP) by echocardiogram. The drug group showed a significant reduction in heart rate from 95.1 ± 8.2 bpm to 71.1 ± 6.2 bpm ($p < 0.001$). This group also showed significant improvement in 6-min walk distance and dyspnea on modified Borg scale ($p < 0.001$) at 6 months follow up. However no significant difference was found between both groups regarding PASP or FEV1 at 6 months.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the most common cause of Cor pulmonale. Patients with chronic obstructive pulmonary disease (COPD) commonly have tachycardia. Norepinephrine spill due to chronic hyoxia in COPD leads to increased sympathetic tone (increased sympathetic discharge or stimulation) and acceleration of heart rate.[1] This increases with frequent use of bronchodilators (β2-agonists, theophylline and steroids).[2]

Pulmonary hypertension is the underlying pathologic mechanism of right ventricular hypertrophy in cor polmonale. Heart rate reduction in patients with pulmonary hypertension may be useful and various potential mechanisms have been postulated.[3]

Ivabradine selectively and specifically inhibits funny current (If), a primary sinoatrial node pacemaker current, reducing heart rate at rest and during exercise. There is no negative inotropic effect or blood pressure reduction with ivabradine compared with beta-blockers and non-dihydropyridine calcium channel blockers.[4] Heart rate reduction with ivabradine has been found to decrease morbidity and mortality among patients with heart failure with reduced ejection fraction.[5] The purpose of this trial was to study the effect of heart rate reduction with ivabradine on the symptoms, functional capacity and pulmonary artery pressure in patients with COPD with Cor Pulmonale.

2. Methods

We selected 162 patients of COPD (symptoms and FEV1/FVC <70%) with Cor pulmonale (clinical features and PASP >30 mmHg) that presented to the Cardiology department at SS Hospital, BHU from May 2018 to April 2019 after baseline screening. Subjects were enrolled if they fulfilled the following criteria: stabilised with inhaled bronchodilators ± steroids for COPD exacerbation and diuretics for right-sided heart failure, normal sinus rhythm and a heart rate of more than 90 bpm. Exclusion criteria were known concomitant coronary artery disease, hypotension (SBP<100 mmHg), left ventricular systolic dysfunction on echocardiography (left ventricular ejection fraction <50%), significant (moderate-severe) valvular heart disease and inability to sign informed consent.The study was approved by the ethics committee in our institution. All patients provided signed informed consent.

After baseline screening and fulfilling all criteria 100 subjects were randomly allocated on a 1:1 basis into drug group (Ivabradine 5 mg twice daily) and control group (placebo). All enrolled patients underwent evaluation at baseline and at 6 months. Evaluation of all enrolled patients was done by following methods:

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- Dyspnea was classified using a modified Borg scale where 0 = no dyspnea, 1 = very light dyspnea, 2 = light dyspnea, 3 = moderate dyspnea, 5 = intense dyspnea, 7 = very intense dyspnea, 9 = very, very intense dyspnea and 10 = maximum dyspnea.[6]
- Pulmonary function tests: forced vital capacity (FVC), forced expiratory volume in the first second of the forceful exhalation (FEV1) and FEV1/FVC ratio.
- 6-min walk test[7] performed in an enclosed corridor (crash trolley with available oxygen supply nearby) − the patient was asked to walk as far as possible in 6 min. The distance they had walked was measured.
- A standard 12 lead ECG was recorded, mean RR length was calculated using a digital calliper software system[8] and heart rate was determined using the formula: heart rate = 60/RR.
- Echocardiographic examination: a standard two dimensional echocardiography machine (Seimens, Acuson) was used to measure the following:
    - left ventricular ejection fraction − by teicholtz method.
    - pulmonary artery systolic pressure (PASP) - by utilising the simplified Bernoulli equation from the peak tricuspid regurgitant velocity and adding this to an estimate of right atrial pressure.
    - Tissur doppler derived E/E′
    - Doppler derived LVMPI as described by Tei.[9]

2.1. Statistical analysis

Continuous variables were presented as mean ± 1 standard deviation (SD) and categorical variables as numbers and percentages if normally distributed. Comparisons between the items were made by chi square and student's t-test. Statistical software namely SPSS 16.0 and Systat 8.0 were used for analysis of data.

3. Results

We randomised 100 patients into the drug group (50 patients) and control group (50 patients). Table 1 shows baseline

Table 1
Baseline characteristics of control and drug groups.

	Control (n = 50)	Drug(n = 50)	P value
Age	58 ± 8	56 ± 8	0.81
Male gender (n)	25 (50%)	29 (58%)	0.72
Smoking(n)	48	47	0.98
Hypertension (n)	5(10%)	6(12%)	0.91
Diabetes(n)	5(10%)	5(10%)	1.0
Modified borg scale	5.1 ± 1.4	5.3 ± 1.3	0.91
BMI(kg/m$^{2)}$	25.6 ± 5	26 ± 4.1	0.38
SBP (mmHg)	120.2 ± 10	122 ± 9.2	0.35
DBP (mmHg)	79.1 ± 11	78.9 ± 8	0.41
Heart rate (bpm)	96.2 ± 11	95.1 ± 8.2	0.52
6MWD (m)	232.2 ± 66.1	220.2 ± 68.1	0.67
LVEF (%)	65.2 ± 6.1	68 ± 7.2	0.31
PASP (mmHg)	42.2 ± 14.1	43.1 ± 13.2	0.29
FEV1(L)	1.38 ± 0.66	1.37 ± 0.52	0.89
FEV1(%predicted)	41.12 ± 18.1	40.9 ± 15.9	0.33
Treatment of COPD/Cor pulmonale			
Beta 2 adrenergic agonists, n (%)	50 (100%)	50 (100%)	1.0
Steroids, n (%)	35(70%)	38(76%)	0.86
Anticholinergic agents, n (%)	38(76%)	36(72%)	0.9
Diuretics, n(%)	32(64%)	37 (74%)	0.36

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; 6MWD = 6-min walk distance; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; FEV1 = forced expiratory volume in first second.

characteristics of both groups. There were no significant differences between the 2 groups with respect to clinical, echocardiographic, pulmonary function and treatment data at baseline (Table 1).

Clinical assessment was done by measuring the heart rate, modified borg scale for dyspnoea and 6 min walk distance. The drug group showed a significant reduction in heart rate from 95.1 ± 8.2 bpm to 71.1 ± 6.2 bpm (p < 0.001) with no significant change in heart rate in the control group. This heart rate reduction was associated with improvement in modified Borg scale score (Fig. 1) and 6-min walk distance (Fig. 2) compared with the control group.

Table 2 shows the echocardiographic parameters and FEV1 at 6 months follow up between the two groups. No statistically significant difference was found between both groups regarding echocardiographic parameters or FEV1 at 6 months. The drug group showed mild adverse effects in the form of blurred vision (8%), sinus bradycardia 50−60 bpm (5%) and headache (3%).

4. Discussion

In this study, we tested the effect of reducing heart rate with ivabradine on the functional capacity as well as effect on PFT and echcocardiographic parameters.The main symptoms were dyspnea and exercise intolerance as a result of occlusive airway disease. Most patients were on bronchodilators and other supportive medications like diuretics for symptomatic relief. Both groups showed relatively rapid heart rate (96.2 ± 11.0 bpm versus 95.1 ± 8.2 bpm; p = 0.52). Several factors are responsible for rapid heart rate in COPD patients.

In our study, the use of ivabradine was associated with a reduction in heart rate and significant improvement of modified Borg scale and 6-min walk distance. Ivabradine reduced heart rate from 98.2 ± 7.2 bpm to 72.8 ± 6.1 bpm. KMahmoud et al[10] also showed that Ivabradine 7.5 mg twice daily for 2 weeks improved exercise capacity in COPD patients.Tachycardia can reduce the exercise tolerance in COPD patients by increasing myocardial oxygen demand and decreasing coronary perfusion time. Shortened diastole also causes incomplete relaxation between beat resulting in an increase in diastolic pressure relative to volume.[4] In COPD patients, control of excessive tachycardia due to combined sympathetic overstimulation and frequent use of sympathomimetics may be beneficial in improving exercise capacity. Ivabradine was studied in patients with heart failure with reduced ejection fraction in the SHIFT study.[11] The use of ivabradine was associated with a significant improvement in New York Heart Association class, a reduction in admission due to all-cause and any cardiovascular disease and reduction in mortality due to all causes and any cardiovascular disease. Previous studies have demonstrated that resting heart rate is a risk factor for mortality in COPD.[12]

We did not find any significant difference between both groups regarding FEV1 as ivabradine has no effect on pulmonary
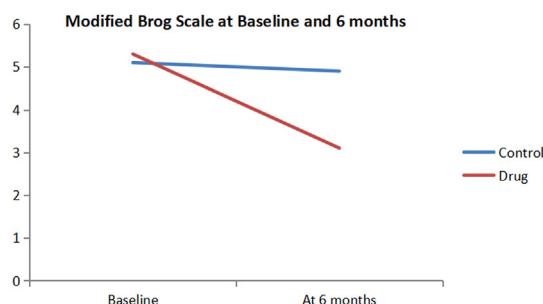

Fig. 1. Change in modified Borg scale from baseline to 6 months follow up (p < 0.001).
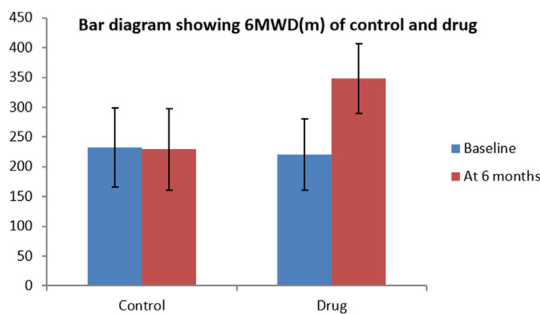
Fig. 2. Bar diagram sowing 6MWD (m) of control and drug group (p < 0.001).

Table 2
Comparison of echocardiographic and PFT data between control and drug group at 6 months follow up.

	Control (n = 50)	Drug(n = 50)	P value
LVEF (%)	63.1 ± 7.1	66.2 ± 8.1	0.19
E/E'	6.2 ± 3.2	6.3 ± 3.4	0.56
LVMPI	0.47 ± 0.18	0.48 ± 0.19	0.51
PASP (mmHg)	44.0 ± 13.2	40.0 ± 12.8	0.07
FEV1(L)	1.36 ± 0.64	1.35 ± 0.51	0.12
FEV1(%predicted)	40.12 ± 18.6	41.2 ± 16.1	0.18

LVEF = left ventricular ejection fraction; E/E' = ratio of peak E velocity in meters per second and early diastolic E' on TDI; LVMPI = Left ventricular myocardial performance index; PASP = pulmonary artery systolic pressure; FEV1 = forced expiratory volume in first second.

function.[13] There was no significant difference between the two groups regarding the pulmonary artery systolic pressure despite the above mentioned significant improvement in clinical condition. G.Tytova et al,[14] however, in one study showed that early prescription of ivabradine in patients with chronic cor pulmonale and right heart failure prevents worsening of RHF by improving the structure-functional data of the right heart chambers, which has a positive influence on life quality of these patients. One study in COPD stage III-IV patients showed the use of ivabradine was associated with statistically significant lowering of pulmonary hypertension, heart rate and increase of exercise tolerance without negative effects on myocardial contractility, electrophysiological parameters, or data of spirometry.[15] KMahmoud et al[10] showed that Ivabradine 7.5 mg twice daily for 2 weeks improved exercise capacity without a change in pulmonary artery pressure and systolic and diastolic function of heart. In a clinical study, Ivabradine was administered to 10 PAH patients with HR > 100/min for 3 months, and along with a significant reduction in HR, exercise tolerance and mean NYHA functional class were significantly improved, whereas PAP remained unchanged.[16] At this moment it remains to be fully examined whether heart rate reduction with ivabradine is useful for pulmonary hypertension in COPD patients. This notion remains to be examined in randomized clinical trials in future studies.

In our study, ivabradine was relatively safe with no severe adverse events.

5. Conclusion

Heart rate reduction with Ivabradine can improve the clinical status and exercise capacity in COPD patients with cor pulmonale. The drug however did not affect pulmonary function (FEV1) and pulmonary artery pressure (PASP) in these patients. It was safe and well-tolerated in COPD patients.

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