Original article

Role of Sildenafil in treating Pulmonar H pertension in COPD patients

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Running title: Sildenafil can help patients having COPD-PH.

Abstract

Backgro nd: Pulmonar h pertension (PH) is a common accompaniment in COPD. It causes functional jeopard and affects the survival of COPD patients.

Methods: 55 patients of advanced COPD (GOLD III and IV) having PH (on a composite clinic-radio-echocardiographic criteria) were treated with sildenafil when the failed to show significant improvement on optimal COPD management including the best possible rehabilitation as per the working protocol of the institute. The effect of the intervention was assessed in terms of change in pulse rate, SaO2 (both resting and after a defined exercise) along with CAT (COPD assessment tests) score after 5-6 months of treatment.

Res lts: An improvement was observed in all the parameters with the CAT score showing a significant difference ($P < 0.05$) in the qualit of life both including and excluding the patients having exacerbations.

Inference: Pharmacotherapeutic intervention of pulmonar h pertension in COPD patients having persistence of s mptoms despite treatment appears worthwhile in terms of the improvement in the qualit of life measured b CAT score. Further research is recommended to establish the role of the drug to treat COPD-PH.

(The Pulmo - Face; 14:2, 41-45)

ABBREVIATIONS:

COPD: Chronic Obstructive Pulmonary Disease

PH: Pulmonary Hypertension

PAP: Pulmonary Artery Pressure

RHC: Right Heart Catheterization

HRCT: High Resolution Computerized Tomography

QOL: Quality of Life

CAT: COPD Assessment Test

6MWT: 6 Minute Walk Test

OSA: obstructive sleep apnoea

DPLD: diffuse parenchymal lung disease

DE: Doppler echocardiography

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INTRODUCTION:

The prevalence of PH in advanced COPD has been found to be quite significant but the raised pulmonary artery pressure (PAP) is mostly mild and sometimes moderate [1, 2, 3]. Suspicion of PH is possible form clinical and radiological pictures and further substantiation can be done by doppler echocardiography although the right heart catheterization (RHC) remains the gold standard for the confirmation-of pulmonary hypertension [4]. Here we present the experience of treating a selected cohort of advanced COPD patients (GOLD III and IV) with pulmonary hypertension been diagnosed on a composite clinical, radiological, and echocardiographic criteria.

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METHOD:

Selection of patients: Advanced COPD patients (GOLD III and IV) diagnosed on spirometry observing the ATS guideline [5] were included from the out-patient department following procuring proper written informed consent for evaluation and treatment of pulmonary hypertension on a real world prospective protocol. The study was approved by the registered institutional ethics committee. Patients with severe co-morbid states affecting the quality of life adversely, very advanced COPD with inability to follow up or perform spirometry, patients with history of exacerbation in the preceding six weeks, and patients unwilling to give written informed consent were excluded. The co-presence of any other pulmonary disease (viz., DPLD) (diagnosed clinicoradiologically or with spirometry) that can cause dyspnoea and hypoxemia were excluded. All the patients thereafter were looked for the presence of pulmonary hypertension on a defined protocol.

Diagnosis of PH: the presence of PH was considered according to the protocol followed in the institute [6] that includes at least one response been positive from each of the following as a) clinical: advanced COPD (GOLD III/IV) patients having significant shortness of breath (MRC III / IV) showing a reduced arterial oxygen saturation (less than 92 % in room air) or a desaturation

of at least a 3% on walking a distance of 15 yards or less in the consultation chamber, b) radiological: (i) agreement of two physicians regarding pulmonary arteries appearing large at hila with or without right ventricular enlargement on chest X-ray (PA view), and / or (ii) HRCT showing pulmonary artery root diameter being same or bigger than the aortic root diameter, or (iii) the pulmonary artery to bronchus ration being 1 in 3 or 4 lobes as measured on their end on shadows, and c) doppler echocardiography showing the pulmonary artery systolic pressure being 40 mm of Hg measured by a single expert on a particular machine (HP sono-7005h, Aligent Technology, USA) in the morning hours following a rest of 30 minutes in order to minimize the chance of exercise induced rise in the pulmonary artery pressure, if any. The echocardiographist was kept blind about the patients' details. Oxygen supplementation was offered as and when necessary while doing the echocardiography.

Right heart catheterization was optional and was kept reserved for those who were willing to undergo the test.

Consideration of treatment of PH: all the patients selected had received an optimal management for COPD that included pharmacotherapy (as per guideline recommendations), treatment of co-morbidities, 'the best possible' pulmonary rehabilitation under the circumstances with long term oxygen therapy in indicated cases. For logistic constraints, the institute observes a self formulated rehabilitation protocol (referred to as 'the best possible' rehabilitation effort). It incorporates COPD related education formatted in a syllabus using a booklet elaborating all basic elements of COPD therapy (from smoking cessation, lifestyle modifications, exercise training, proper use of inhalers and breathing exercises to use of home oxygen therapy in indicated cases) in a group meeting. The patients are also explained the use of the inhalation devices, bronchial hygiene and breathing exercises with one to one demonstrations. The intervention also includes a special effort to stimulate motivation for self managed practice of the imparted education and training. We have successfully utilized this model in our rural COPD program too [7].

The decision of treatment for PH was considered if a patient had significant and persisting symptoms with poor health status (CAT score more than 12) despite optimum COPD management with pharmacotherapy and 'the best possible' rehabilitation efforts as mentioned above for six weeks. In cases of persistence of severe symptoms (functional class IV), resting hypoxemia (SaO_2 92 % at room air), and clinically overt right heart failure, the anti –PH therapy was initiated early.

Treatment protocol for PH: Sildenafil, (Assurans 20 mg tablets, Cipla Ltd. Mumbai) was prescribed orally as 10 mg every 8 hours to start with. The dose was increased to 20 mg 8 hourly the next over one to two weeks. The patients were instructed to stop the medicine in case of worsening of symptoms or having a new symptom / difficulty after starting the drug. A very special caution was raised to those taking nitrates for ischemic heart disease. In them, whenever possible, nitrates were substituted by ranolazine. All the patients were made aware of the adverse reaction of sildenafil with instructions to look for the side effects (especially the postural symptoms) and contact us.

The impact of the treatment was measured in terms of the change in pulse rate, SaO2 (at rest and after a defined exercise in the consultation room), and CAT (COPD assessment test) score measured at the initiation and on the first follow up visits. There was no compulsory follow up protocol in this real world study; rather, the patients were suggested to come as and when necessary and at least once after 12 weeks according to their convenience. Exacerbations during the period of follow up and the adverse reactions were noted.

Results and analysis: Statistical analysis were done to see a) the change in QoL through the change in the CAT scoring and b) the change in resting and exercise SaO2 and pulse rate after treatment with sildenafil using the paired Student's *t*-test. The adverse events and the drop outs were also recorded.

RESULTS:

A total of 65 patients qualified for use of sildenafil in a period between March, 2012 and March, 2013. Out of the 55 patients consented for the trial of sildenafil, six had dropped out for no improvement or worsening of symptoms before the first follow up. 7 patients could not continue the medicine regularly (three for financial reason, two for local non availability of the medicine, and in three, the medicine was stopped by some other doctor for surgery or some other reasons). Out of 42 patients one person died for unrelated reason, eleven patients stopped the treatment (one for headache, six for increased shortness of breath, and uneasiness in three). We could collect the follow up CAT score in 30 subjects and the statistical analysis was done with their data only. The result shows the following characteristics of the patients as a) the Mean age 66.6 ± 10.8 years, b) the mean systolic PA pressure 46.83 ± 6.74 mm Hg, c) the mean duration of receiving sildenafil 146 ± 117.02 days, and d) the mean post bronchodilator FEV_1 as 29.92 ± 14.86 % of predicted with the mean value being 0.76 ± 0.31 Litres. The pre and post medication comparison reveals positive but not significant improvement in the pulse rate and saturation but a significant ($p< 0.05$) change in the CAT scoring (see table 1)

DISCUSSION:

COPD is a chronic debilitating disease with progressive and poorly reversible airflow limitation. PH is a known complication of COPD [1, 2, 3] and it occurs in two clear subsets of the diseased population. The prevalence of PH in mild to moderate COPD is not known though very infrequently, some of these COPD patients show severe PH and this subset is regarded by some as a distinct entity [4, 5]. However, PH in severe COPD is noted frequently (30 – 70 percent) in several studies [1, 2, 3]; the PH in most of these patients is usually mild.

Incidentally, in our study population all the patients of COPD were of severe nature with mild PH as per the used diagnostic criteria. The mean systolic PAP (calculated) was found to be more than 25 mm of Hg using the formula derived from Chemla D et al. [8] in our patients qualifying for therapy.

Parameters	Pre medication (n=30)	Post medication (n=30)	p-value
Pulse rate (/min)	85.71 ± 15.89	83.75 ± 11.25	0.62
SaO2 (%)	93 ± 5.38	94.04 ± 5.09	0.49
CAT	20.2 ± 4.53	16.84 ± 5.32	**0.02**

Table 1: shows change in pulse rate (rest), SaO_2 (rest), and CAT score before and after treatment with sildenafil.

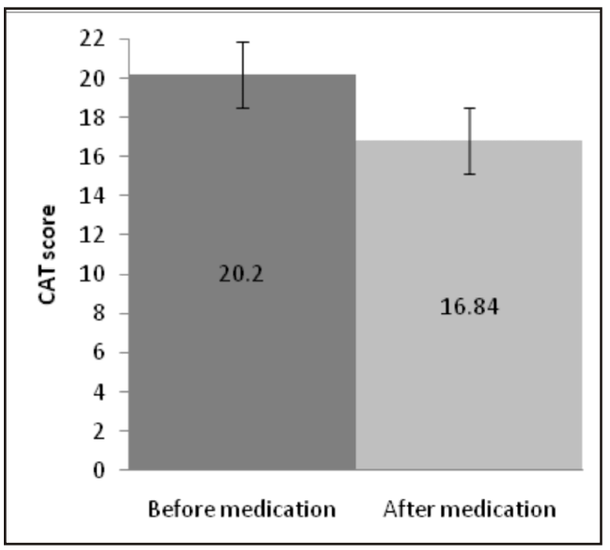

Fig re 1: elaborates the change in CAT score through bar chart in patients of COPD-PH been treated with sildenafil.

Diagnosis of PH in COPD is essentially done by right heart catheterization (RHC) [9, 10]. Doppler echocardiography (DE) has shown serious limitations in predicting PAP with low sensitivity, specificity, and predictive value in patients with COPD [11]. This is largely because of the technical difficulty to get a good echo window in COPD patients. Overall DE has a success rate of 26-66% in COPD patients to correctly estimate the RV systolic pressure [12, 13]. Incidentally PH with COPD has significant clinical implications since it can cause functional limitation [14] and affect the survival adversely [15, 16]. Therefore, reduction of PAP is an obvious therapeutic target and such interventions should come through recommendations based on good studies with hemodynamic parameters being monitored through RHC.

But simply for logistic reasons, in our part of the developing world, the use of RHC is grossly restricted. Hence, we decided to use a composite clinico-radio-echocardiographic criteria to diagnose PH in our COPD subjects as discussed in the methodology. We have been using this criteria in our publications [6]. The reasoning is that the presence of features of PH in both in chest x-ray (PA) and HRCT with Doppler echocardiography showing a peak pulmonary artery systolic pressure over 40 mm of Hg. should naturally have a higher diagnostic accuracy than echo features alone as several measurements in chest x-ray and the HRCT chest have shown high diagnostic specificity for PH [17]. We could not uniformly measure the main PA diameters on chest X-rays since, in real world, the available digital x-ray plates were of different sizes. Hence, we tried to improve our acumen of radiological interpretations with the pooled opinion of two observers (two pulmonologists or a pulmonologist and a radiologist all being blinded about the patients). Pulmonary arterial prominence at hila was accepted when more than one observer noted so. We included the HRCT chest in our diagnostic exercise since it has specific signs (100% specificity) for the presence of pulmonary hypertension. These signs are: a) the mean pulmonary artery diameter > 29 mm [18] or b) the ratio of the transverse diameter of a pulmonary artery to that of adjacent bronchus being more than 1 in three or four lobes, [19] and c) the diameter of the PA root appearing wider than or equal to the diameter of aorta [19].

Keeping in mind the importance of PH in COPD as a co-factor for functional jeopardy and poor survival [14, 15], we decided to look for the possible benefits of the available anti-PH treatment to the small cohort of our advanced (severe) COPD patients having PH. They had gross functional limitation with persistence of symptoms despite optimum pharmacotherapy along with the best possible efforts for rehabilitation under the given circumstances.

Optimum general care and pharmacotherapy of COPD, smoking cessation and pulmonary rehabilitation should be done before embarking upon PH specific therapy. Long term oxygen therapy has been found to have a beneficial role in COPD-PH [20, 21, 22]. In our cohort, we have offered optimal COPD management with education and exercise training and motivation for self managed practice of rehabilitation efforts with use of long term oxygen therapy.

The role and the indication of PH specific therapy is not property defined for PH with COPD. However, it has been suggested in situations as persistent PH despite the best possible therapy and in PH disproportionate to the lung function [23]. We considered anti-PH pharmacotherapy categorically in those patients who had either advanced disease with advanced functional jeopardy (MRC III and IV) without improvement of subjective (both physician and doctors) and objective (pulse rate and SaO2 at rest and after small walking) parameters on treatment. We, however, did not look for repeating echocardiography to see the improvement.

Upon the diagnosis of PH as per the laid out criteria, we decided to use sildenafil following an informed written

consent. PH specific therapy in patients with COPD has been attempted with several agents as NO (nitric oxide) [24, 25], bosentan (endothelin receptor antagonist) [26], PDE 5 inhibitor as sildenafil [27, 28, 29], and prostacycline analogue [30, 31]. The choice of using sildenafil was simply because it appeared economic than bosentan the other available drugs in the market. Incidentally, we did not come across any severe side effects except for headache (two), increased shortness of breath (six), and uneasiness (three). In some of them, though the drug could be restarted with proper counseling and precaution, the subjects were left out of the statistical analysis. None of our patient had any visual or hearing problem, one patient complained of headache in whom the agent was withdrawn and there was no documented hemodynamic problem in any.

People have tried to treat PH in COPD. A randomized trial with bosentan in 30 severe COPD patients (6 had PH in resting echocardiography) showed no significant functional benefit [26] and in them SaO2 and QoL declined compared to those taking placebo. However, a small series have shown potential benefit of using sildenafil in PH with COPD [27, 28]. It was found that use of sildenafil could alter the exercise induced rise of PAP in a small group (n=18) of severe COPD patients with PH [29]. Treatment of secondary pulmonary hypertension in COPD is also tried with prostacycline (30, 31). There was no improvement in stroke volume and exercise capacity with sildenafil in another group of patients of PH with COPD [32].

The treatment of PH in COPD includes treatment of co-morbidities as OSA, DPLD, left heart disease and pulmonary embolism if present. In our cohort, none of the patients had radiological DPLD (an exclusion criteria), clinically suspected OSA or suspicion of pulmonary embolism. Moreover, the echocardiography done actually ruled out presence of any significant left heart disease or systolic dysfunction. However, left ventricular diastolic dysfunction was present in 60 % of our cases. Incidentally, this has been regarded as a cause of PH and this area needs in depth study.

There are some other weaknesses too in our study. The most important has been the lack of RHC data for diagnosis and assessment of the response to therapy. To our mind, although we cannot specifically note the mean pulmonary artery pressure value, the diagnosis of PH was fairly certain since we included clinical, chest X-ray, HRCT and echocardiography findings together. However, it remained impossible to learn the exact degree of PH in these patients. Concomitant post-treatment echocardiographic data could have been an effective adjunct in the study. Observing the long term effect of sildenafil in such cohort will remain a future area of interest. The dose of sildenafil was restricted to a maximum of 20 mg 8 hourly; this could have left the therapeutic benefit to a sub-maximal level; one need to see the dose-effect relationship of this anti-PH therapy in COPD.

Despite these limitations, the best strength of the study is to ethically face the question of not denying the benefit of the available treatment of PH in our advanced COPD population just for short of RHC data. In this area of debate, to the best of our judgments, we can stand the ethical challenge and our view is also been seconded [33]. Further research is required to find a simple algorithmic approach to validate the composite diagnostic criteria for PH – comparing it with RHC values of PAP and other hemodynamic parameters. There may be questions regarding our 'the best possible' rehabilitation effort; we could try the best feasible actions in the context of the ground reality where the prescribed pulmonary rehabilitation was not possible or feasible. Despite all, our observations reveal a horizon of offering relief of symptoms and functional benefit to a huge number of patients of COPD without subjecting then for invasive tests especially in resource constraint context.

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