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Abstract

Background: Treatment of Class III pulmonary hypertension that can affect the oxygenation and quality of life may be worthwhile.

Objective: To identify class III pulmonary hypertension programs are not feasible and virtually not exercised in a tertiary pulmonary OPD practice and observe the effect of treating them with sildenafil on defined indications.

Methods: Multiple single point intensive education on COPD were imparted along with formatted training on major elements of rehabilitation as use of inhalation therapy, respiratory exercise and life style modification etc. on a cohort of rural COPD population in several rural areas of the developing world.

Results: 81 patients (mean age 62.43±10.17 years) from different etiologies have been recorded to have documented follow up on sildenafil. COPD (35.7%), past history of tuberculosis (21%), indeterminate etiology (13.5%), DPLD (13.5%), and asthma (11%) remain the major causes of pulmonary hypertension. There has been universal improvement across the different causes with the mean CAT score reducing from 15.33±5.52 to 13.01±5.79 (p=0.004) and the mean arterial oxygen saturation improving from 94.6±2.90 to 95.05±3.12 percent. The improvement in CAT was significant for COPD (p=0.03, n=29).

Conclusion: Single point, intensive education and rehabilitation intervention appears significantly effective in rural COPD population in allaying symptoms and improving the perception of the health status over a period of six weeks.

KEY WORDS: COPD, pulmonary rehabilitation, VAS (The Pulmo -Face, 2014; 14:1, 10-14)

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ABBREVIATIONS:

KEY WORDS: pulmonary hypertension, pulmonary artery pressure, quality of life, CAT (The Pulmo -Face, 2014; 14:1, 5-9) 14:1, 5-9, 10-14

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INTRODUCTION:

Pulmonary hypertension (PH) is not uncommon in different respiratory disorders including OSA. It affects the QoL adversely. The diagnosis of PH appears greatly restricted in the developing world for lack of RHC as recommended by the guidelines. Thus, possibly, a huge number of patients are deprived of the likely beneficial effects of anti PH treatment. Amidst scanty data from the Indian subcontinent, the actual prevalence of PH attending pulmonologists is not negligible. The existing guidelines are not very clear to recommend the medical therapy of class III PH from different causes. Here, we present our initial experience of a real world study of looking at the effect of sildenafil on selected class III PH patients in a pulmonologist’s day to day practice without adopting RHC.

METHODS:

The study was performed in a referral pulmonary OPD, Kolkata, India observing a real world protocol being approved by the institutional ethics committee. The method included a) Selection and confirmation of class III PH, b) selection of candidates for anti PH therapy and prescription of sildenafil, and c) observation of the efficacy of treatment in terms of QoL (quality of life) and change in oxygenation (arterial oxygen saturation) with concomitant recording of the adverse and the serious adverse events.

a) Selection and confirmation of PH: The diagnosis of pulmonary hypertension was made at the institute following an indigenous clinic-radio-echocardiographic criteria (without doing right heart catheterization).

The diagnostic approach was initiated with suspicion of PH from clinical suspicion, or having any known co-morbidity of cardiac problem apparent from the chest x-ray (done on clinical suspicion), or having any known co-morbidity of respiratory disorders including OSA. It affects the QoL adversely. The diagnosis of PH appears greatly restricted in the developing world for lack of RHC as recommended by the guidelines. Thus, possibly, a huge number of patients are deprived of the likely beneficial effects of anti PH treatment. Amidst scanty data from the Indian subcontinent, the actual prevalence of PH attending pulmonologists is not negligible. The existing guidelines are not very clear to recommend the medical therapy of class III PH from different causes. Here, we present our initial experience of a real world study of looking at the effect of sildenafil on selected class III PH patients in a pulmonologist’s day to day practice without adopting RHC.

METHODS AND MATERIALS:

Inclusion criteria: Patients of either sex aged more than 40 years with or without history of active smoking but with history of progressive shortness of breath, cough and/or expectation for over 2 years were screened for presence of COPD. Those who show feature of airflow limitations (FEV1/FVC < 70 %, and FEV1 < 70 %) without reversibility (less than 10 % increment of peak expiratory flow rate after 20 minutes of 4 puffs of salbutamol with a spacer) were regarded as cases of COPD.

Exclusion criteria: Patients with recurrent purulent expectation, clinically detected clubbing/ cyanosis or any skeletal deformity, known or suspected ischemic heart disease, congenital or valvular heart disease apparent in clinical examination, any other significant pulmonary or cardiac problem apparent from the chest x-ray (done on clinical suspicion), or having any known co-morbidity of significant dimension, were excluded from the study. Very sick patients, those unable to perform spirometry or unwilling to give consent were also excluded.

Since it is not possible to adopt a formal COPD rehabilitation that requires a lot of organizational input and economic commitments, we decided to make a single point intervention of education and training based on a simple curriculum. This was prepared with our background experience of teaching COPD patients attending our OPDs and training camps incorporating the basic issues as proper inhalation technique, breathing exercise, walking, nutrition etc. On a follow up visit after 6 weeks of such intervention we assessed the situation based on visual analogue scale (VAS).
The past experience of doing several COPD education and training camps with publication of a booklet as a part of our institutional activities helped us to form a lot of literature, print and publish a simple curriculum in Bengali (with pictures describing several exercises and inhalation devices and their uses) for the population to address and also to plan the actual course of action foreseeing the planned camps. The curriculum also provides a review of what to do and what not to do for the patients. It includes practical and essential elements on areas as a) about the disease with role of smoking in its pathogenesis, b) when to suspect and diagnose COPD, c) what happens in COPD to the lungs and what are the symptoms, d) what a patient of COPD should know, e) how to use inhalers, f) required lifestyle modifications as smoking cessation, exercise, proper food, avoidance of smoke and irritants, and use of oxygen when required.

We experimented the booklet in our conventional COPD camps and became confident and apt in using it to a gathering of patients with or without audio visual assistance.

b) Reaching to the target population was possible through the infrastructure and man power help of an organization (West Bengal Liver Foundation) engaged in rural based epidemiological work and the involvement of our consultant in Rural Bengal, Suri, Birbhum. Ten volunteers, chosen from the WBLF, were trained beforehand to suspecting COPD patients in villages based on appropriate response to a set of simple questions (not yet validated) and bringing them (about ten patients each) to the camps at purse in summer and winter time respectively.

C) Actually performing the job: a) fixing a venue: mostly the municipality building or school (in weekends) where a big room being fixed for a common address, b) making arrangements with three spirometers and Indian chest Society certified trained technicians, c) joining our doctors and two trainers from our WBLF team, d) actually performing the physical examination of patients with or without audio visual devices and their uses) apt for the population to address and also to plan the actual course of action foreseeing the planned camps. The curriculum also provides a review of what to do and what not to do for the patients. It includes practical and essential elements on areas as a) about the disease with role of smoking in its pathogenesis, b) when to suspect and diagnose COPD, c) what happens in COPD to the lungs and what are the symptoms, d) what a patient of COPD should know, e) how to use inhalers, f) required lifestyle modifications as smoking cessation, exercise, proper food, avoidance of smoke and irritants, and use of oxygen when required.

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The patients with overt right ventricular failure or functional class IV status with resting saturation being less than 90 percent with PH been quite evident were directly taken up for PH therapy. PH therapy with sildenafil with concomitant optimization of the treatment for the etiology with or without advice of hospitalization.

The patients with history of any sure or suspected history of sildenafil toxicity or intolerance or allergy to the agent and the patients on concomitant use of nitroglycerines were excluded. Any patient with pregnancy, lactation, or having any significant systemic disease was excluded from the study at the beginning.

All the patients were discussed about the potential and known side effects of sildenafil and requested to report any suspected or sure side effects while on treatment. Apart from this, telephonic enquiries were done to all after 15 days of the start of the treatment for any intolerance/adverse events. The dose to start with was 10 mg thrice daily and it was hiked to 20 mg thrice a day on tolerance after 3 to 7 days.

c) Observation of the efficacy of treatment: The quality of life was assessed at the initiation and after 12 weeks of treatment in terms of CAT score by a single experienced clinical assistant. The adverse events and the serious adverse events were also recorded.

RESULTS:

The project was initiated on 2nd week of January, 2013 and by the end of December, 2013, a total of 145 patients were prescribed sildenafil of which 81 patients completed the follow up at 12 weeks after starting the anti PH therapy. Out of the total number, 18 patients dropped out for various reasons (six for headache and seven for pedal edema, three for uneasiness and two for increase in breathlessness). One patient stopped the treatment for unknown reason. 45 of the patients are yet to complete the visit after 12 weeks. The Table 1 elaborates the spirometric lung function values, the quality of life in terms of CAT score, the pulmonary artery systolic pressure (in Doppler echocardiography), the adverse events and other parameters been listed under the common etiological headings. When a patient had more than one possible reason for having PH, the predominant one as per the investigator has been listed. Incidentally, we could get anaesthesia. A total of 175 patients attended the camps before repeat doppler-echo study been done in 13 patients compilation of data. Out of them 40 patients were excluded observing a common protocol by the sameet al. [6] had severe dyspnoea, 4 had active eosinophilia, 3 had suspected / proved active tuberculosis, 8 had findings suggesting clinically significant some other diseases. The patients with acute exacerbation of the disease problems were referred to the local/district Govt. Hospitals. Thus, 135 patients were finally diagnosed COAD and all of them agreed to undergo the study and to mark their symptoms on VAS.

RESULTS:

The pooled data from three such camps were collected for the analysis. A total of 175 patients attended the camps before repeat doppler-echo study been done in 13 patients compilation of data. Out of them 40 patients were excluded observing a common protocol by the sameet al. [6] had severe dyspnoea, 4 had active eosinophilia, 3 had suspected / proved active tuberculosis, 8 had findings suggesting clinically significant some other diseases. The patients with acute exacerbation of the disease problems were referred to the local/district Govt. Hospitals. Thus, 135 patients were finally diagnosed COAD and all of them agreed to undergo the study and to mark their symptoms on VAS.

In the same, use of inhalers and respiratory exercise (diaphragmatic breathing and breathing with positive expiratory pressure – ‘pursed leap’) are demonstrated. One or two patients are usually selected randomly to repeat the procedure so to ensure the attention of the audience to register the issues in their minds. Free questions regarding the disease, the treatment and the demonstrated exercises were allowed thereafter.

6) Following that the team gets divided into 3 groups to check inhalation technique in one to one fashion and re-educate on breathing exercise. We used only DPI (with lupihaler, Lupin Pharma) for the purpose.

7) Drug distribution: We arranged for 15 days course of DPI for all the patients who attended and needed the drug. The travel cost was also reimbursed at this point.

8) It was followed by tea and a food packet. They were told to revisit us after 6 weeks on a fixed date.

FOLLOW UP:

The patients were followed up after 6 weeks in another subsequent camp when we arrange a rehearsal of inhalation, exercise and education on a common gathering along with rectifying flaws, if any in the techniques. The impression of symptoms as shortness of breath, cough, wheeze and overall health status being perceived by each patient were all recorded on VAS.

The mean age of the patients included for analysis was 56.58 ± 9.66 years with the sex ratio (male: female) was 3.2: 1.3. The mean duration of symptoms was 15 ± 6.12 years. Hence, only 45 patients were incorporated for the final analysis. The age, sex, smoking history and spirometric values of the patients are given in the Table 1.
was somewhat restricted for logistic reasons. It is possible cases; surely we missed many conditions as the protocol also not a well documented and recognized entity to cause lung function as DPLD having a similar FVC (55 % vs. 55.77 ± 21.22) suggesting that the chronic asthmatics milder disease (FEV1/FVC = 83.62 and % of FEV1 being 51.24 ± 11.19 litres) have severe disease (FEV1/FVC = 64.63 and % of FEV1 being 61.78 ± 37.81).

Looking at the lung function, the COPD patients appear to have a place in the international classification of PH (13, 14). We could not find out the cause in 13.5 % of cases; surely we missed many conditions as the protocol.

DISCUSSION:

There have been two important outcomes from the study. First, the COPD remains the commonest cause of PH (35.8 %) to pulmonologist in referral practice and that this co- incidental finding lead us to separate the COPD phenotype by lung function are the unlikely to have severe PH. The rural areas of the developing world regarding the epidemiology of COPD is scanty, that has been found significant and the overall perceived evidence in favor of rehabilitation is so strong rehabilitating programs in rural India.

In India, the dimension is quite huge in 42.09 ± 18.73 years respectively. All male patients active or ex smokers while the female subjects too were smokers (n=2). Very few were aware about their comorbidities in one, is chemic heart disease in two (hypertension in one, diabetes due to shortness of breath or suspected pneumonia. The mean BMI was 17.11 ± 0.59; speaking about the poor nutritional status of the selected participants. Spirometric data analysis showed the mean FEV1/FVC ratio to be 51.24 ± 42.33; the change in the VAS scoring has been found significant and the overall perceived well being has been seen to be 21.22 ± 9.49 litres and 67.53 ± 17.97 %.

Table 1: The CAT score and the spirometric status (post bronchodilator) of the patients of PH been included for treatment with sildenafil (with the standard deviation for the applicable parameters have been provided with ± values).

Table 2: Comparison between initial and final CAT score

**DISCUSSION:**

The table 1 shows the change in symptoms and the perceived sense of wellbeing before and after 6 weeks of intervention. There has been a significant improvement in the well being of symptoms and perceived well being (see table 1).

With the standard deviation for the applicable parameters have been provided with ± values.

Table 1: Mean scoring on VAS of symptoms and perceived well being (see table 1).

The change in the VAS scoring has been found significant and the overall perceived well being has been seen to be 21.22 ± 9.49 litres and 67.53 ± 17.97 %.

Since the burden of COPD is so huge (2, 3) and the evidence in favor of rehabilitation is so strong (9, 10, 11, 12)
The second important information derived from our observation is that there has been a universal and statistically significant ($p=0.004$) improvement in QoL in all the patients as a group. However, the change has been different in PH patients with different etiologies and when seen individually with different number of patients in each subgroup, despite being universal, the improvement is significant statistically only in COPD patients. The drug has been well tolerated with a total of 19 adverse events (AE), 14 hospitalizations from unrelated cause (not related to sildenafil) of which one succumbed. One very sick patient died at home before hospitalization. The commonrehabilitation program has also been found comparable to hospital based program. Duration wiser, even a shortened 4-week supervised pulmonary rehabilitation program is as effective as a 7-week supervised programme at the comparable time points of 7 weeks and 6 months.

The next argument evolves an ethical issue to treat patients without RHC data as no guideline accepts the presence of PH is certain in our patients through the available evidences for the diagnosis of PH from chest x-ray (PA view) and HRCT chest; these evidences have strong specificity for the presence of pulmonary hypertension. This was further supported by echocardiographic diagnosis of PH. Such diagnosis based on clinically radio-echocardiographic criteria implies that the assessment of the exact pulmonary artery pressure is not possible.

The next argument involves an ethical issue to treat patients without RHC data as no guideline accepts the diagnosis of PH without RHC. To us, withholding the administration of anti-PH therapy cannot be justified any longer especially for people who are sick enough (WHO visual analogue scale has been in use to assess several functional class III or IV) despite the optimum treatment of disease entities; the beauty being its simplicity to use, the underlying conditions. These issues had been conducted to see the relative power of outcome measured at the time of presentation to the Ethics Committee meeting where we could convince the most frequently used and validated variables as members regarding our stand to remain humane in treating the patients even in the absence of RHC data using HRQoL. Health-related these patients on a defined real world protocol in addition to COPD education and training for self managed care and rehabilitation in rural areas on a curriculum covering the major important issues related to the disease in simple question-answer forms. The area of operation and the manpower support were thoughtfully selected in collaboration with the West Bengal Liver Foundation. Finally, a structured modus operandi was prepared through repeated discussions and interactions amongst the working members keeping the logistics and expected practical problems in view. Perhaps, the key to success of such a program has been the appropriate training and mobilization of the manpower concerned according to the perceived scenario.

There may be questions about a) diagnosis of PH, b) Indication of therapy, c) dose and choice of the drug, and d) The assessment tool. We admit that we had to deviate a lot from the guideline recommendations that included RHC universally for diagnosis. Our argument takes into account the available evidences for the diagnosis of PH from chest x-ray (PA view) and HRCT chest; these evidences have strong specificity for the presence of pulmonary hypertension. This was further supported by echocardiographic diagnosis of PH. Such diagnosis based on clinically radio-echocardiographic criteria implies that the presence of PH is certain in our patients through the assessment of the exact pulmonary artery pressure is not possible.

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There may be questions regarding the duration of optimum therapy for the underlying diseases. We took a cut off at peak exercise, 6MWT, and CRQ may be the best value of 2 weeks (except for very sick patients with obvious practical tools to evaluate responsiveness to PR). To us it appeared that further delay may jeopardize the purpose of such treatment and it also been found to be better in asthematics than in COPD looked unlikely for a patient to show at least the beginning subjects, we choose to see the effects on VAS alone of improvement further on optimum treatment of the although concomitant assessment with other valid underlying condition beyond this period. The next question parameters like SGRQ, 6MWT, BDI/TDI, etc could have involved was the treating agent and the dose. We had been better. Using VAS happened to be the most feasible chosen sildenafil (a phosphodiesterase-5 inhibitor) as an option to assess the changes in symptoms (dyspnea, used widely elsewhere and has been easily available with the subjective perception of the a relatively low cost in the market. We have kept the dose of the overall health status for such single point intervention in fixed for comparison; although further hiking the dose in the rural COPD population, some patients could have yielded a better result. The incorporation of the history of pulmonary tuberculosis in the etiological classification of Class III PH is a new addition in the list of etiologies.

Although tuberculosis has not been officially recognized as a cause of PH, we have shown that the significant positive impact in several parameters as patients form a good bulk (21%) of the PH population in rural COPD rehabilitation program in rural areas. Effort intensive program at the primary care with implementation
Regarding assessment of a patient of PH, right heart catheterization and hemodynamic data appear important but are not mandatory as per the guideline recommendations. Tests like six minutes walk test, cardiopulmonary exercise testing, universal repeat echocardiography could have been worthwhile adjuncts to the CAT score. Incidentally repeat echocardiography was possible in 13 of our patients concomitant to the repeat recording of CAT score. The observed echocardiographic improvement in terms of the measured PAP (systolic) has been found to go parallel to the improvement in CAT score (figure 2). For logistic reasons we could not measure anything else but CAT score. This is a validated instrument to measure the health status of the COPD patients, and it has also been used in DPLD successfully. (18) Till date, there has been no data available regarding its use in OSA, or other lung conditions causing shortness of breath with jeopardy in lung function. We have chosen CAT for its simplicity, our expertise in using the instrument, and to maintain uniformity in recording the health status in several conditions. The number of patients been observed is small COPD sufferers. Some additional interventions as supply and it is difficult to compare the effect of sildenafil between the different etiological subgroups although it appears from the results that the effect is positive in all the etiological categories.

Despite the weaknesses been mentioned it appears that constrained people. A systematic record with a much the treatment of symptomatic class III PH patients with a higher number of recruits with an impact of the result sildenafil remains helpful in terms of improvement in the several factors as monthly income, family status, QoL. Prima facie, the proposed clinic-radiological educational status etc. could have been definitely better to echocardiographic criteria appears acceptable although it provides an insight regarding their compounding effects on needs validation before widespread recommendations the intervention. Moreover, we did not incorporate an intervention along with the pharmacotherapy in our rural conditions. The number of patients been observed is small COPD sufferers. Some additional interventions as supply and it is difficult to compare the effect of sildenafil between the different etiological subgroups although it appears from the results that the effect is positive in all the etiological categories.

We feel it necessary for the medical intelligentsia to appreciate and formulate guideline for diagnosis and treatment of class III PH in our country based on the feasibility of investigations in face of resource constraints.

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