Effect of Sildenafil Citrate on Pulmonary Arterial Systolic Pressure and Sub-maximal Exercise Capacity in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background

Pulmonary hypertension (PH) often complicates Chronic Obstructive Pulmonary Disease (COPD). Sildenafil reduces pulmonary arterial pressure associated with multitude of diseases.

Objective

To evaluate the use of Sildenafil in Pulmonary Hypertension associated with COPD.

Method

This randomized control study enrolled 72 patients: 61 completed the study. Thirty-patients with COPD received Sildenafil 25 mg thrice daily and 31 patients with COPD received optimal medical therapy for four weeks. Symptom assessment and dyspnoea grading was done with modified Borg scale and Modified Medical Research Council (MMRC) grade. The functional assessment was done with WHO functional classification. The estimation of pulmonary arterial systolic pressure and six minute walking distance was done before and after four weeks of the administration of therapy in both groups. Adverse reaction profiling was done for Sildenafil. The primary outcomes were the changes in pulmonary arterial systolic pressure and six minute walk test. The secondary outcomes were change in modified Borg scale for dyspnoea, MMRC grading and WHO functional class.

Result

The mean decrease in pulmonary arterial systolic pressure in Sildenafil group was significant as compared to controls (9.87+7.84 mmHg Vs 5.93+7.44 mmHg, P=0.048). The mean increase in six minute walk distance was significantly more in cases as compared to controls (48.13+25.79 m Vs 32.59+32.96 m,P=0.047). The changes in modified Borg scale was not significant (1.20+1.92 to 1.55+1.23; P=0.401). There was significant changes in MMRC grade (p=0.037). There was no significant change in WHO functional class after four weeks (p=0.071).

Conclusion

Sildenafil marginally decreased pulmonary arterial systolic pressure and increased six minute walk distance in COPD patients. It improved MMRC grading without affecting modified Borg's Scale and WHO functional class.

KEY WORDS

Chronic obstructive pulmonary disease, Pulmonary hypertension, Sildenafil, Six minute walk distance

INTRODUCTION

Pulmonary Hypertension (PH) remains the important long term squeal of Chronic Obstructive Pulmonary Disease (COPD).[1] In advanced COPD the prevalence of PH is between 30-50%.[2] Echocardiographic prevalence of cor-pulmonale is around 27.3%.[3] PH is reported to double mortality over five years in COPD.[4] Shorter survival, more frequent exacerbations, increased use of health resources and exercise impairment are the common outcomes.[5-8]

World Health Organization (WHO) group one PH has received much attention with treatment options targeting Endothelin, Nitric oxide and Prostacyclin pathways.[9,10] These medications improve hemodynamics, exercise tolerance, delays worsening and mortality.[11] Among these, Sildenafil is commonly available and medically approved in Nepal.[12] With no approved pharmacological treatment long-term oxygen therapy (LTOT) appears as the only modality proved to slow the progression.[13-16]

In COPD the synthesis of nitric oxide in pulmonary arteries is impaired. Hence, Sildenafil can be of benefit.[17] Consequently, the growing interest.[12] Oral pulmonary vasodilators improve oxygenation in WHO group III PH.[18,19] Sildenafil improves pulmonary hemodynamics at rest and during exercise but impairs arterial oxygenation at rest. Hence, the cautionary advice for close monitoring.[11] Sildenafil in PH-COPD has shown variable effects on exercise tolerance, blood gases and ventilation perfusion even with significant decline in mPAP.[11,20]

Worldwide data available on use of medication for PH-COPD is lacking, which is further enhanced in South East Asian Region (SEAR).[21] There are PH-COPD patients in Nepal without much improvement in the functional status. Reduction of PAP in PH-COPD may be the missing link in the conventional therapy.

To explore the possible routine use of Sildenafil in PH-COPD, we hypothesized that Sildenafil might improve outcome of these patients in terms of reduction of PH with subjective improvement in dyspnoea, oxygenation, and exercise tolerance.

METHODS

This was a prospective randomized control study conducted in two tertiary referral centers in Kathmandu: Shree Birendra Hospital (SBH), Chhauni and Bir Hospital, National Academy of Medical Sciences (NAMS). Seventy-two patients were enrolled during the study period of two years. Study population was grouped into two. Sildenafil group received oral Sildenafil citrate in the dose of 25 mg TDS for the period of four weeks along with all the standard treatment modalities for COPD. The control group received standard optimal therapy of COPD for the period of four weeks including LTOT.

Subjects diagnosed with COPD on relevant history and spirometries were included. All grades of COPD (I, II, III and IV) under optimal medical therapy and LTOT with frequent exacerbations were included. WHO functional class of PH I, II and III with echocardiography evidence of PASP >36 mmHg was the major inclusion criteria.

The exclusion criteria were: anaphylaxis or allergic reactions to Sildenafil Citrate, fall in blood pressure of >30 mmHg systolic or >20 mmHg diastolic after intake of the first dose of Sildenafil and pulmonary hypertension other than that due to COPD. Patients with significant left sided cardiac disease (LVEF <45%, cardiomyopathy, valvulopathy, coronary arterial diseases) were also excluded. Patients with WHO Functional Class IV were excluded, as they were too breathless for any activity. Patients receiving treatment with nitrates and other specific drugs for reducing arterial PH in the last four weeks were excluded. Pregnancy, major systemic diseases, malignancy, liver or kidney disease where also excluded.

All patients presenting to emergency department or out patient service of department of respiratory medicine were screened for presence of PH. The subjects were asked to fill and state their MMRC grade and Borg scale scoring at the time of enrolment. WHO-FC was identified for all the subjects. Reassessment was done on weekly basis till the end of the four weeks.

Study group assignment was done randomly. The random numbers were generated by computer based random number generator and sequential allotments were done. Total 36 cases and controls were enrolled.

SMWT was performed two times in a subject: at the time of enrolment and after four weeks. The SMWT was performed indoors per ATS guidelines.[22] The study subjects were asked to score the level of dyspnea with modified Borg scale (MBS), before and after the SMWT. The functional exercise capacity was compared using distance walked (in meters) before and after the study period. Echocardiography (ECHO) was done to quantify the PASP: first at the time of recruitment and second at the end of the fourth week. Oxygen saturation was measured with pulse-oximeter at all visits.

Hemodynamic changes were measured in terms of heart rate (HR), respiratory rate (RR) and blood pressure (BP) during the first 24 hours of the study. These parameters were reassessed weekly there after till the end of the study. When the participant developed severe side effects, mainly hypotension, the drug was stopped and he/she was disqualified from the study.

All the participants were followed up in the first 24 hours of the administering the drug and weekly thereafter. All contact details including telephone and mobile numbers were utilized to contact the participants if they were not on regular follow up.

Two groups were statistically analyzed using independent t-test for the comparability. A p–value of <0.05 was considered as statistically significant. Zero week and four week values of ECHO estimated PASP, SMWD, MBS, MMRC grade and WHO-FC were evaluated using paired t-test and their differences evaluated for statistical significance in individual study groups. The difference between 0 to 4 week values of all the four parameters was compared between the two groups to find their statistical significance by independent t-test. Initial data tabulation was done in Microsoft Excel 2010. All the data were analyzed digitally using IBM SPSS Statistics version 20.

The identities of the patients were kept confidential. All the patients enrolled were required to provide informed written consent at the time of enrolment. All the patients had the option to opt out of the study at any time during the period of the study. The study involved intervention in the form of use of FDA and DDA approved medication during the study period. All the enrolled patients received standard treatment for COPD. The expense of the standard COPD treatment of SBH patients was borne by SBH as per protocol, and was free of cost to the patient. The ethical clearance was taken from the Institutional Review Board (IRB) of NAMS, Bir Hospital.

RESULTS

At the end of two years study period data were completed for 72 subjects. There were 36 in each case and control groups. However, only 30 subjects in Sildenafil group and 31 subjects in control group completed the study. The total numbers of mortality, lost to follow up population, drop outs and acute exacerbations in the study and control groups are given in figure 1.

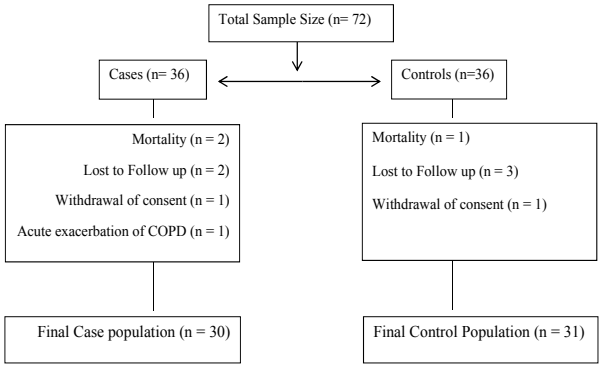

Figure 1. Enrolment and selection of case and control population for the study.

The mean age of the study population was 64.2±5.01 years. Age distribution varied from 50 to 74 years. The baseline characteristics of the treatment and control groups are enlisted in table 1.

Pulmonary Arterial Systolic Pressure: The mean PASP (mPASP) for the treatment group was 75.9±17.89 mmHg and 69.77±11.61 mmHg for the controls at the onset.

Table 1. Baseline characteristics of the study population

Characteristics	Cases	Control	P value
Total number	30	31	
GOLD II	8	7	0.121
GOLD III	11	15	0.082
GOLD IV	11	9	0.114
Age	63.47±5.99 years	64.93±3.74 years	0.260
Sex ratio	1:1.1	1:1.2	0.452
Smoking	26 smokers	25 smokers	0.718
FEV1/FVC	56.24±13.89%	54.29±9.82%	0.528
FEV1	0.63±0.18 L	1.01±0.25 L	0.072
FEV1%	37±11%	54.9±14.6%	0.089
FVC	1.17±0.34 L	1.84±0.21 L	0.092
Mean PASP	75.9±17.89 mmHg	66.77±11.61mmHg	0.122
SMWD	202.06±70.52 m	163.67±82.32 m	0.572

There was no statistical difference in the two groups of the study population at the onset of the study (p=0.122). The mPASP after four weeks period was 62.17±14.87 mmHg with minimum value of 36 mmHg and maximum 95 mmHg. The mPASP for treatment group and control group were 66.03±19.62 mmHg and 63.84±5.82 respectively.

The mPASP decreased from 75.9±17.89 mmHg to 66.03±19.62 mmHg in cases (p<0.001) in four weeks. The mPASP decreased from 69.77±11.61 mmHg to 63.84±5.82 mmHg in controls (p=0.153) in four weeks.

The maximum decrease in PASP after four weeks was 27 mmHg and maximum increase in PASP was 15 mmHg. There was significant difference between cases and controls after four weeks. The mean decrease in the PASP was more in cases than controls (9.87±7.84 mmHg Vs 5.93± 7.44 mmHg). This difference was statistically significant with p=0.048. The first and fourth week data on PASP is enlisted in table no. 2.

Table 2. Echocardiography changes in PASP during study period and statistical significance of the differences

Group	Group A (cases)	Group B (Controls)	P value between groups
0 week	75.9±17.89 mmHg	69.77±11.61 mmHg	0.122
4 week	66.03±19.62 mmHg	63.84±5.82 mmHg	0.095
Difference of means (0 to 4 weeks)	9.87±7.84 mmHg	5.93±7.44 mmHg	0.048
P value with in group (0 to 4 weeks)	<0.001	0.153	

Six Minute Walk Test and Distance: The mean SMWD was 182.87±78.43m at the beginning of the study. The Sildenafil group had SMWD of 202.06±70.52m and controls had SMWD of 163.67±82.32 m. There was no statistical

difference between cases and controls at the beginning of the study (p=0.57). After four weeks of treatment the cases and controls were again subjected to SMWT. The mean SMWD at this instance was 223.23±78.82 m. The mean SMWD for Sildenafil group was 250.2±74.1 m and the mean for control population was 196.27±75.12 m. There was statistical difference between cases and controls at the end of four weeks (p=0.007). The mean SMWD increased from 202.06±70.52 m to 250.2±74.1 m in cases (p<0.001). The mean SMWD increased from 163.67±82.32 m to 196.27±75.12 m in controls (p=0.007).

The mean change in SMWD for the case population was 48.13±25.79 m. The mean change in SMWD for the control population was 32.59±32.96 m. The minimum increase of SMWD in case group was 10m whereas maximum increase was 112.2m. The minimum change in control group was the decrease of SMWD by 50 m whereas maximum change was the increase in SMWD by 87 m. The change in SMWD of the cases and controls were evaluated and was found to be marginally significant with p=0.047. This data is further explained in table no. 3.

Table 3. Six minute walk distance before and after study period of 4 weeks.

Group	Group A (Cases)	Group B (Controls)	P Values between groups
SMWD (0 Week)	202.06±70.52 m	163.67±82.32 m	0.572
SMWD (4 Weeks)	250.2±74.1 m	196.27±75.12 m	0.007
Difference of means (0 to 4 weeks)	48.13±25.79 m	32.59±32.96 m	0.047
P value with in group (0 to 4 weeks)	<0.001	0.007	

Modified Borg Scale for perceived dyspnoea: At the onset of the study mean pre-test Borg scale value for Sildenafil group was 4.07±2.22 and control group was 3.74±0.89. After four weeks the mean pre-test Borg scale value for case group was 2.87±1.63 and control group was 2.19±0.94. There was no statistical difference between cases and controls with respect to Modified Borg Scale at four weeks (p=0.056). Pre and post-test Borg scale (after SMWT) value for Sildenafil group and control group is given in table no 4 with respective p values.

WHO functional class for PAH: At the time of enrolment into the study total seven patients (11.4 % of total) were in class II: four in Sildenafil group (6.5% of total) and three in control-group (4.9% of the total). Total 54 subjects (88.5 % of total) were in class III: 26 in Sildenafil group (42.62% of the total) and 28 in control group (45.9 % of the total). None of the subjects were in class IV. There was no statistical difference between the class distribution of the cases and controls (p=0.718) at the start of the study.

At the end of four weeks the WHO functional status was reclassified for each subject. There were total 31 subjects

Table 4. Modified Borg Scale values before and after study period of 4 weeks

Group	Group A (cases)	Group B (Controls)	P values
Pre-test BORG (0 Week)	4.07±2.22	3.74±0.89	0.462
Pre-test BORG (4 Weeks)	2.87±1.63	2.19±0.94	0.056
Difference of means(0 to 4 weeks)	1.20±1.92	1.55±1.23	0.401
P value with in group(0 to 4 weeks)	**p=0.002**	**p=0.001**	
Post-test BORG (0 week)	6.50±2.37	7.45±2.03	0.098
Post-test BORG (4 weeks)	5.40±2.26	5.42±1.56	0.969
Difference of means (0 to 4 weeks)	1.10±2.52	2.03±2.12	0.123
P value with in group (0 to 4 weeks)	**p=0.024**	**p=0.001**	

in Class II (50.8%): 19 in Sildenafil group (31.1%) and 12 in control (19.6%). There were total 30 subjects in class III (49.1%): 11 in Sildenafil group (18.03 %) and 19 in control population (31.1 %). There were no subjects in class IV. There was no statistical difference between the cases and controls at the end of the study (p=0.071).

The change in the WHO functional class of the study population was evaluated at the end of four weeks. Total of 37 subjects (60.6% of the total) did not show any change in functional class at the end of the study period. This included 15 subjects (24.5%) in Sildenafil group and 22 subjects (36.06%) in control group. Total 24 subjects (39.3%) showed decrease of function class by one category. This included 15 subjects (24.5%) in Sildenafil group and 9 subjects (14.7%) in control group. This change in functional class was not significant between cases and control (p=0.114).

The changes in total number cases in various WHO-FC from zero week to four week was significant (p<0.001). The changes in total number of controls in various WHO-FC from zero week to four weeks was significant (p=0.001). However, there was no significant changes in WHO-FC after four weeks when compared between cases and controls (p=0.071).

MMRC grading: At the start of the study total of 14 subjects (22.9% of the total) reported dyspnea of MMRC 4 including five subjects in Sildenafil group (8.19%) and nine in control group (14.7%). There were 41 subjects (67.2%) who reported dyspnea of MMRC 3 which included 23 cases (37.7%) and 18 controls (29.5%). There were only six subjects (9.83%) with dyspnea of MMRC 2 which included two cases (3.2%) and four controls (6.5%). There was no

statistical difference of distribution of case with respect to MMRC grading (p=0.377).

The subjects were asked to grade their breathlessness on weekly visits. There was no statistical difference between the cases and controls on first week (p=0.637), second week (p=0.112) and third week (p=0.212) follow up. However, at the end of four weeks there was statistical difference between cases and control on MMRC grading (p=0.037).

The changes in total number of cases in various MMRC grade from zero week to four week was significant (p<0.001). The changes in total number of controls in various MMRC grades from zero week to four weeks was significant (p=0.001). There was significant changes in MMRC grade when compared between cases and controls (p=0.037).

There were total of 33 subjects (54.09% of total) who did not report any change in the grade of their breathlessness. This included 15 cases (24.5%) and 18 controls (29.5%). Twenty subjects (32.78%) showed one grade decrease in MMRC. This included 15 cases (24.5%) and five controls (8.19%). Only one subject (1.6%) showed one step worsening of MMRC scale. This patient was from control population. None of the cases reported worsening of breathlessness as per MMRC grade. Total of seven subjects (11.47%) showed two step decrease/improvement of MMRC scale: five controls (8.19%) and two cases (3.27%). The difference of change of grades for breathlessness as per MMRC was significantly different in cases as compared to controls (p=0.04).

Assessment of Symptoms and adverse drug reaction

The adverse symptoms observed during the study period between Sildenafil group and control groups are enlisted in table 5 with respective p-values.

DISCUSSION

PH-COPD though a major cause of mortality and morbidity, has no effective medical treatment. Drugs used for group one PH, when used for PH-COPD, have shown deleterious effects on gas exchange. On the contrary PDE-5 inhibitors have been shown varying results.[23]

PDE-5 inhibitors have been found efficacious for group one PH.[12] It is known to induce pulmonary vasodilatation by increasing nitric oxide concentration via stabilization of cyclic guanosine monophosphate. Similar physiology may possibly work in severe COPD with the use of PDE-5 inhibitors.[24] With this background our study evaluated the use of Sildenafil citrate 25 mg thrice a day along with optimal medical therapy and LTOT for PH-COPD. A similar case control trial done by Lederer et al. in included ten patients with cross-over design.[25] Similar to our study, sample size of 63 was used by Blanco et al. for his study on pulmonary rehabilitation on PH-COPD. However, this study followed up the patients for longer duration of three months and was placebo controlled.[20]

Sildenafil citrate, being the most readily available medication for PH in Nepal, its evaluation in PH-COPD was conceptualized with the view that it would decrease hypoxic pulmonary vasoconstriction.[26] Several studies in the last decade have evaluated the utility of PDE-5 in PH-COPD.[20,27-29] A crossover study done by Ghofrani et al. showed that pulmonary artery pressure can be reduced by oral intake of Sildenafil and that this decrease in pressure is accompanied by an increase in exercise capacity.[30] The acute beneficial effect of Sildenafil on pulmonary artery pressure during sub-maximal exercise in COPD patients was confirmed by Holverda et al.[31] On the contrary, several studies did not show functional benefit of PDE-5 in PH-COPD.[28,29] And concerns were raised that treatment with a PDE-5 inhibitor could worsen hypoxemia owing to hypoxic vasoconstriction inhibition in COPD patients.[11,32]

With the inconclusive reports on the use of Sildenafil Citrate in PH-COPD, the assessment tools were re-evaluated to include sub-maximal exercise capacity instead of maximal exercise, since maximal exercise capacity is limited by ventilation and not by circulation in the majority of the patients of COPD.[8,26] Hence, many studies used SMWD as the measure of sub-maximal exercise capacity to evaluate outcome in PH-COPD treatment.[24,33,34] With the background of these research our study also took SMWD as the tool for assessment of exercise capacity.[24]

Both the study and control groups in our study were matched with respect to demographic parameters. Rao et al. matched the study groups with respect to age, FEV1, SMWD and PAP at baseline. These characteristics were also matched in our study population.[34]

Park et al. studied the functional impact and improvement of PH-COPD with St. George Respiratory Questionnaire (SGRQ).[24] No change was identified in SGRQ scores after the completion of the study period. This study did a subjective assessment of breathlessness with Borg scale and found no change before and after the study. In accordance with the study our study also did not show any statistical improvement of Borg scale at the end of the study period.[24]

There was significant subjective improvement of self-reported breathlessness as assessed by MMRC grading in Sildenafil group in our study. However, there was no statistically significant change in WHO-FC in case population as compared to control population at the end of study period. Unlike our study, in a study done by Wong et al. patients with PAH were given Sildenafil for three months.[35] It was observed that the 6MWD and WHO functional class of dyspnea improved even without any significant improvement in PAP. This suggested a possibility that apart from effect on PAP Sildenafil might have an additional physiological effect. However this study was not specifically conducted for COPD patients with PAH.[35] Similar to our study, Rietema et al. found no improvement in the Borg dyspnoea index after 12 weeks of Sildenafil treatment.[29]

Our study also evaluated the new onset symptoms and adverse reactions that were likely to occur with Sildenafil citrate in both the groups. Significant number of Sildenafil group reported one or more episodes of syncope during therapy with Sildenafil citrate. Among the other common side effects of Sildenafil, there were significant occurrence of flushing, tremor and diarrhoea. Photosensitivity and other visual abnormalities were never reported by the entire study population during the study duration. Rao et al. showed that epigastric discomfort, headache, paresthesia and numbness as the adverse events in the study population.[34] In their study headache was the most common symptom reported by the subjects.[34] In the study done by Park et al. with the use of Udenafil on PH-COPD subjects 26.4% study population dropped out due to adverse drug reactions.[24] There was increase in breathlessness in three subjects. The minor symptoms were nausea, flushing, dizziness, palpitation and abdominal pain. The subjects who developed these symptoms refused the further treatment in this study.[24] Similar to this study, the most common minor symptom in our study population was flushing.

The best prognostic factor for PH-COPD remains mPAP. The five year survival rate is only 36% in patients with initial mPAP>25 mmHg compared to 62% in those with initial mPAP≤25 mmHg.[4] Majority of the patients in our study had higher recordings of PASP than 50 mmHg, which is an ECHO based criteria for likely-PAH.[13] The mean PASP was 72.83±15.27 mmHg. Hence our study focused mainly on severe forms of PH-COPD. For such group of patients LTOT serves as the only beneficial therapy which can reverse the PAH but even that treatment would fail to normalize it.[15,36]

Exercise capacity is dependent on PH: an independent predictor for exercise capacity. This relation was identified by Sims et al.[7] They found that higher PH were associated with shorter SMWD in 362 severe COPD subjects. These subjects underwent right-heart catheterization (RHC) as part of evaluation for lung transplantation. They found an 11 m decline in SMWD for every 5 mm rise in mPAP.[7] In our study linear relation was identified between SMWD and PASP. We found that with every one mmHg rise in PASP there was fall of SMWD by 1.99 m i.e. approximately 2 m. So, if we compare with the Sims et al study every 5 mmHg rise of PASP declined the SMWD by 10 m.[7] However, our study was based on 2D-ECHO estimated PASP and not based on mPAP with RHC as in previous study. Similarly, the records of 1154 COPD patients listed for lung transplantation were reviewed by Cuttica and colleagues. They found association between mPAP and SMWD independent of lung function and PAWP.[6]

Alp et al. were the first to report on the acute and long-term effects of Sildenafil in COPD.[27] They showed significant improvement in both hemodynamic parameters and SMWD in six patients with COPD-PH with Sildenafil for three months. The mean increase in SMWD was 82 m.[27] Unlike this study we selected patients with high PASP and our study followed up the patients for a shorter period of time.

Rietema et al. studied the effects of oral Sildenafil 50 mg thrice daily for 3 months in 15 COPD patients and reported similar results: neither stroke volume nor exercise capacity improved.[29] However, the enrolled subjects had very low mPAP as compared to our study population. In a double-blind, randomised, placebo-controlled trial conducted by Rao et al. there was a significant increase in SMWD from baseline after three months of follow-up in Sildenafil users.[34] The median change in SMWD was 190 m as compared to placebo users. The PAP decreased significantly in Sildenafil group after three months, while it did not change significantly among placebo group.[34]

The study design of this study done by Rao et al. was similar to our study.[34] We also divided our study population into two groups. However, our study was not placebo controlled. In our study control population only received optimal medical therapy along with LTOT. Similarly, our study also took PASP and SMWD as the important outcome parameters. Along with these parameters our study also assessed the subjecting improvement of symptoms and breathlessness with Borg Scale, MMRC and WHO functional classification. However, this study had two follow up time assessment. First they followed up study population at the end of first month, similar to our study. In addition to this they followed up the study population after three months which we did not do. Our study period was shorter by two months as compared to this study. Even with shorter period of study our study showed marginally significant improvement of SMWD in Sildenafil group (from 202.06±70.52 m to 250.2±74.1 m i.e. 48 m increase). The control group also showed improvement in SMWD from 163.67±82.32 m to 196.27±75.12 m, i.e. 32 m increase. Unlike our study the placebo group in the Roa et al. study showed median increase of SMWD by 15 m after three months.[34] The increase in SMWD in Sildenafil group when compared with control group was statistically significant in our study which was in accordance to this study.[34] Rao et al. concluded that Sildenafil citrate improved SMWD and decreased PASP in patients with severe COPD which was also true for our study.[34]

The change of 48 m in SMWD seen in our study is generally considered an acceptable and clinically significant change.[37] Puhan et al. study on interpretation of treatment changes in SMWT found that 35 meters change for SMWD for any given person is an important effect.[38] In addition Holland et al. study published in 2010 showed that 25 meters was the minimal important difference for SMWD in COPD.[39]

Physiologically, PDE-5 inhibitor could worsen hypoxemia owing to inhibition of hypoxic vasoconstriction in COPD patients, with relative increase in perfusion of ill ventilated areas worsening ventilation/perfusion (V/Q) mismatching.[11] In our study there was no acute decrease in SpO_2 in both

cases and control population during the study period. There was in fact slight improvement of SpO_2 from baseline in Sildenafil group which was statistically significant as compared to control group at the end of first week. In fact, meta-analysis done by Jinkyeong Park and colleagues on PH-COPD has shown no worsening in oxygenation during PH-specific treatment. This suggested a minimal adverse impact on V/Q matching in COPD.[40]

There were few limitations in our study. First, recruitment process spanned almost two years. As we were conducting research on COPD patients with documented high PASP not getting better with optimal medical therapy, to find suitable candidates who would tolerate relatively high doses of Sildenafil Citrate itself was a difficult process. Hence, there was no one time recruitment as for a closed study design. This selection might have introduced bias. In addition, this was a relatively small double centre study, and the results need to be confirmed in a large-scale randomized study.

The primary investigators were fully aware of the whole screening, recruitment, treatment, complications and outcomes in both case and control population. The cardiologists who agreed to be the part for performing 2D ECHO on the subjects were specifically asked to look for PASP during recruitment and follow up. They were aware of the subject's pre-study values while performing post-study PASP. Hence, this was not a single or double blinded study. Blinding was also not ethically feasible on these subjects, as they were relatively sick subgroup of COPD patients.

Right heart catheterization was not performed during our study. PASP was measured by echocardiography. It is known that the estimation of PASP by 2D-ECHO is frequently associated with inaccuracies.[41] 2D-ECHO estimation of PASP was used in our study as it is an easy and non-invasive method with a good correlation with right heart catheterization.[42,43]

Our study was limited with respect to follow up duration. We followed up all the cases and controls for four weeks. In most of the outcome related studies on PH-COPD or PAH of other groups follow up duration spanned from four weeks,[34] eight weeks,[24] 12 weeks,[34,35] and 18 months.[33] So long term effect of Sildenafil with respect to benefit, morbidity and side effects could not be derived from our study. Few subjects from this study who showed good subjective and objective improvement of signs of symptoms of COPD are still continuing Sildenafil Citrate along with optimal medical therapy. With this study we fail to identity that subset of population who would actually tolerate and benefit from Sildenafil citrate, as it was not prospectively included in the protocol.

Lastly, our study was not a survival analysis with longitudinal follow up. Hence, we are not able to conclude on mortality benefits from Sildenafil citrate.

CONCLUSION

This study showed that Sildenafil Citrate may be used in patients with PH-COPD. The use of Sildenafil citrate decreased subjective sensation of breathlessness as assessed by MMRC scale. There was also small but statistically significant decrease in PASP in COPD with the use of Sildenafil Citrate. There was mean increase of SMWD with the administration of Sildenafil citrate in PH-COPD patients indicating the significant increase in sub-maximal exercise capacity. The effect of this drug was not large enough to cause significant decrease in the WHO-FC for PH and MBS. This drug did not cause severe adverse reactions when given in doses not exceeding 25 mg thrice daily. Minor symptoms like flushing, tremors and diarrhoea were more common but syncope was more distressing to the patient.

Hence, Sildenafil Citrate may be used in severe PH with COPD, which can reduce PASP and increase sub-maximal exercise capacity. Adverse drug reactions can be the limiting factor for its routine use and it requires close monitoring during the initial period of administration.

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