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Research Article

Effects of Tadalafil on the Exercise Capacity and Quality of Life among Patients of Chronic Pulmonary Diseases with Pulmonary Hypertension: A Pilot Study

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Abstract

Objectives: Phosphodiesterase-5 inhibitors (PDE-5) have been reported to be beneficial in improving exercise capacity and quality of life. However, the response of PDE-5 inhibitors in the setting of low atmospheric oxygen tension among natives of medium altitude has not been reported. Present study reports the effect of tadalafil on exercise capacity and quality of life in patients of chronic pulmonary diseases with PH residing at an altitude ranging between 1000 meters to 2500 meters above mean sea level.

Material and methods: Seventy six patients of chronic pulmonary diseases with PH diagnosed by echocardiography were randomized to receive tadalafil 40 mg once a day or to the control group and were followed up for three months. The exercise tolerance was assessed by measuring 6-minute walk distance, Borg dyspnea and fatigue score. The quality of life was measured by St George's Respiratory Questionnaires based scores. The baseline medications were continued during the follow up period in both the groups.

Results: Tadalafil significantly improved the 6-minute walk distance (336.7 ± 63.0 meters vs. 290.7 ± 54.4 meters, $p < 0.001$), Borg dyspnea score (2.9 ± 1.1 vs. 4.0 ± 1.2, $p < 0.005$), and the Borg fatigue score (2.8 ± 1.13 versus 3.8 ± 1.0, $p < 0.005$). The quality of life also improved significantly in the tadalafil group (total St George's Respiratory Questionnaires score 44.3 ± 9.0 vs. 55.8 ± 12.1, $p < 0.0005$). Tadalafil also improved resting and peak exercise arterial oxygen saturation.

Conclusion: In the present study, tadalafil 40mg once daily showed significant improvement in the exercise capacity and quality of life of patients with chronic pulmonary diseases with PH.

Trial registration: Central Trial Registry of India, CTRI/2015/01/005413.

Keywords: *Pulmonary hypertension; Quality of life; St George's Respiratory Questionnaires; Tadalafil; 6-minute walk distance*

Introduction

Chronic pulmonary disease in humans is frequently complicated by the development of pulmonary hypertension (PH), which is associated with increased morbidity and mortality [1]. PH is a chronic syndrome characterised by the progressive deterioration of cardiopulmonary haemodynamics and right ventricular function, leading to impaired exercise capacity and premature death [2]. Hypoxia, inflammation and increased shear stress are the primary stimuli although the exact pathways through which these initiating events lead to PH remain to be elucidated. The increase in PVR is attributed, in part, to the remodeling of the walls of resistance vessels. This consists of intimal, medial and adventitial hypertrophy, which can lead to encroachment into and reduction of the vascular lumen [1]. The normal adult pulmonary vascular bed is a low-pressure, low-resistance, highly distensible system, and is capable of accommodating large increases in

blood flow with minimal elevations of PAP [3]. Echocardiography is a non-invasive method for estimation of the presence and severity of PH. TR velocity derived gradient is the most reliable non-invasive method for estimation of the presence and severity of PH. A TR gradient of more than 46 mm Hg [4] and/or Pulmonary flow acceleration time < 90 msec [5,6] has been taken as an evidence of the presence of PH. The sensitivity and specificity for the detection of PH depends on the cut-off value of pulmonary flow acceleration time.

Tadalafil, a selective inhibitor of cGMP-specific PDE-5, increases the levels of cGMP and thereby enhances nitric oxide-mediated vasodilatation [7]. Alveolar oxygen tension is an important stimulus for the generation of cGMP by smooth muscles of the pulmonary vascular resistance vessels. Tadalafil augments the vasodilatory effect of cGMP by inhibiting its degradation. The longer elimination half-life of tadalafil makes it suitable for the treatment of PH as it can be used as once daily dose [8]. The response of PDE-5 inhibitors in the setting of low atmospheric tension among natives of the medium altitude has not been reported. The present study reports the effect of tadalafil on the exercise capacity and quality of life in patients of chronic pulmonary diseases with PH residing at an altitude of 1000 meters to 2500 meters above mean sea level.

Material and Methods

Study population and selection process: All consecutive patients diagnosed to have chronic pulmonary diseases; for example chronic obstructive pulmonary diseases, interstitial lung diseases and post tubercular pulmonary fibrosis attending the outpatient service of pulmonary medicine were screened for enrolment in the study. Diagnosis of PH was based on the following criteria; TR gradient of ≥ 46 mmHg and or pulmonary flow acceleration time of ≤ 90 msec. Patients of stable chronic pulmonary disease with PH, aged between 20 to 80 years and willingness to participate in the study after informed consent were enrolled. Patients were excluded if they had history or clinical evidence of chronic pulmonary diseases without PH, coronary artery disease, chronic kidney disease, liver disease, left ventricular failure, myopathy/muscular dystrophy, peripheral vascular disease/osteoarthritis of knees, pregnancy, drug history of anorexigens intake, HIV, and were already on tadalafil therapy.

Study period: The study was a pilot study and was conducted from July 2013 to July 2014 with follow up period till October 2014.

Data collection: Data related to socio-demographic characteristics, exposure to risk factors for chronic pulmonary diseases, status of the effort tolerance using NYHA functional class, dyspnea and fatigue score using Borg scale [9] were recorded. The quality of life was assessed using St George's respiratory questionnaire score [10]. Medications prescribed by the treating physician were also recorded and was continued.

Echocardiography examination was done in all patients using an echocardiography machine, Model 1E-33 of Philips Medical System using a broad band phased array adult probe in supine left lateral decubitus position with real time ECG signals to record the following indices of cardiopulmonary haemodynamic parameters:

a. Indices of RV systolic Function.
b. Myocardial performance index (MPI): The MPI is defined as the ratio of isovolumic time divided by ET; [(IVRT + IVCT)/ET]. IVRT (Isovolumic relaxation time), IVCT (Isovolumic contraction time) is the time from tricuspid valve closure to tricuspid valve opening. Right ventricular ET (Ejection time) time interval from beginning of pulse Doppler derived spectral envelop across right ventricular outflow tract (RVOT) to end of the spectral envelop.
c. Pulmonary flow acceleration time (PFAT); Time interval from beginning of the pulse Doppler signal to the peak of spectral envelope at RVOT.
d. Tricuspid Regurgitation (TR) Gradient; Patients with TR in colour flow imaging TR velocity was recorded to Quantify the RV-RA instantaneous peak systolic gradient to estimate PH. TR gradient of ≥ 46 mmHg was taken as the evidence of raised pulmonary artery pressure (PAP).
e. PVR was estimated by recording velocity time integral (VTI) of pulse Doppler spectral recorded in RVOT and maximum TR velocity (TR Vmax)measured by using colour flow mapping guided continuous wave TR Doppler signal and using the formula (TR V max/ RVOT VTI)×10 + 0.16. [6]

f. TAPSE as an index of axial shortening of RV was recorded with M Mode tracing recorded at lateral TV annulus in modified four chamber view.
g. RVFS % was measured by measuring RV dimensions at end diastole and at end systole recorded at the tip of TV leaflet in modified four chamber view using formula RVED-RVES/RVED*100.
h. RV. It is calculated from the parasternal short axis projections as the ratio of the minor axis of the LV parallel to the septum at the level of the chordae, divided to minor-axis perpendicular to and bisecting the septum at the same section.

Six-minute walk test: The six-minute walk test was performed according to American Thoracic Society (ATS) guidelines [7]. At start of the test and at the end of six minutes, the patient's heart rate, blood pressure and oxygen saturation was measured. The patient was asked to indicate his or her "level of breathlessness" by using Borg scale. Subjects were asked to walk as much distance as possible in 6 minutes, at their own pace, and allowed to stop if symptoms of significant distress occurred but were asked to resume as and when possible. 6MWT was repeated after 1 month till three months.

Examination included recording of blood pressure, heart rate, and arterial oxygen saturation with pulse oximeter model: DR-50D made by Dr. Trust. The exercise capacity was measured with recording of the 6-minute walk distance, and severity of pulmonary function compromise was assessed by measuring the lung volumes and flow rates using spirometer model vital graph-Compact-Buckingham, England. The arterial oxygen saturation and heart rate at baseline and at the end of 6-minute walk was also recorded.

Randomization procedure: Patients consenting to participate in the study were randomized after collection of baseline data to either tadalafil or to the control group. The allocation sequence was generated by the physician not involved in the recruitment of the patients using permuted blocks of varying sizes. Randomization was stratified by age groups, sex, and severity of symptoms; NYHA class II or class III. Sequentially numbered, opaque, sealed envelope containing the treatment allocation is prepared by the physician not involved in the study. The envelope was opened after patient's eligibility was confirmed and informed consent was obtained.

Follow up Period: All the patients were closely followed on scheduled monthly follow up visits for three months. The dose of usual care medication was adjusted as per discretion of the treating physician. The medications prescribed by the treating physician were recorded. Eight patients were lost during follow up period.

Outcomes measured: At the end of three months all patients underwent repeat evaluation for exercise capacity and quality of life assessment as at baseline. Investigator measuring the outcome was blinded for treatment assigned.

Statistical analysis: The data was reported as percentages and mean ± SD for categorical and continuous variables respectively. The differences in the distribution of categorical variables among study groups were compared by χ^2 test and unpaired students t-test for continuous variable. 2 tailed significance at value < 0.05 was taken as statistically significant. Data was analyzed using Epi Info version 3.4.3.

Ethical Approval: No. MC Pharma (PF) PG. (Direct)/- 330/13, dated- 04-07-2013.

Results

Baseline clinical characteristics of the study groups: The study groups were well matched for socio-demographic characteristics. The mean age was 61.7 ± 10.1years versus 62.2 ± 10.9 years, p > 0.86 in the control and the intervention group respectively. 51.5% were men in the control group and 57.1%, p > 0.65 in the intervention group. The distribution of exposure to risk factors; tobacco smoke, biomass fuel smoke, duration of exposure, and use of overall bronchodilators and steroid formulations at baseline were similar in the two groups. (Table no.1)

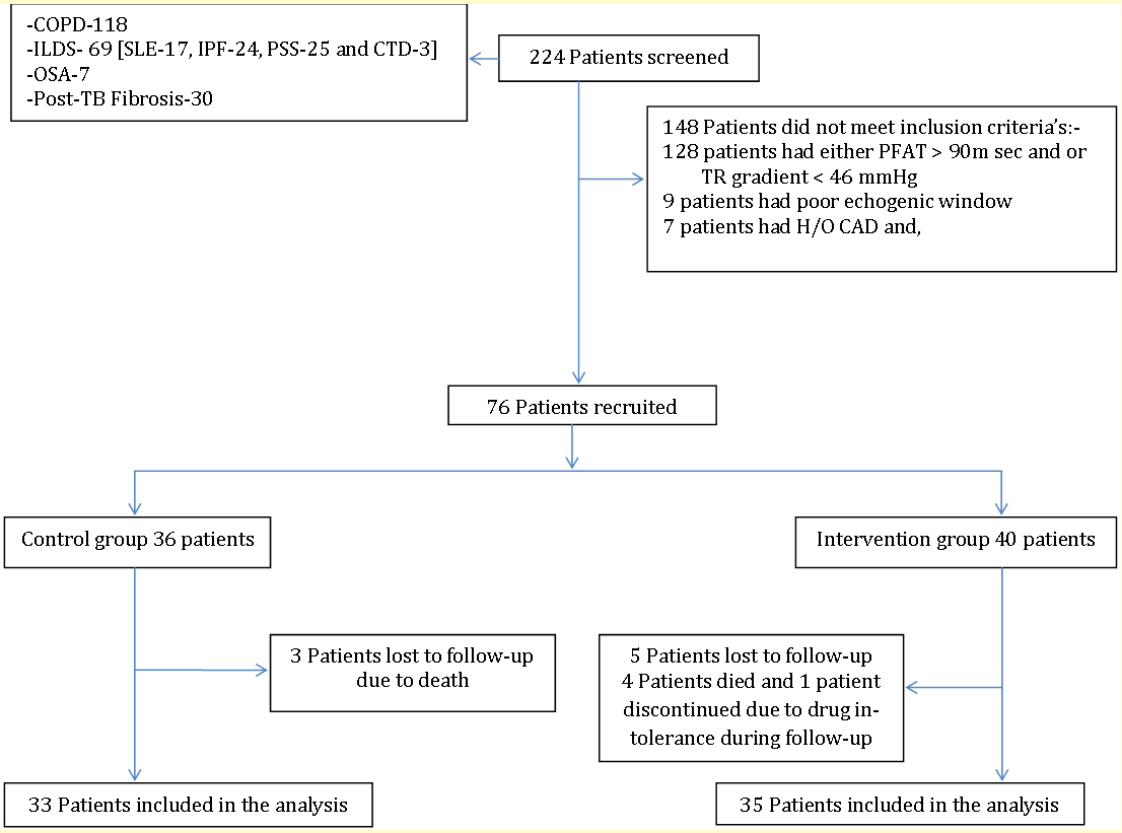

Figure 1: *Flow chart of patients screened, enrolled, randomized and followed up.*

The study groups were well balanced for distribution of severity of NYHA functional class, 6-minute walk distance, dyspnea and fatigue Borg score and also the quality of life scores. The resting arterial oxygen saturation and 6-minute post walk arterial oxygen saturations were well matched in both the groups. The baseline indices of pulmonary function were also similar in both the groups. The mean level of haemoglobin in the study groups was similar 14.9 ± 1.4 vs. 14.9 ± 1.8, $p > 0.9$ in control and the intervention group respectively. (Table no.1)

Characteristics:	Control group (n=33)	Intervention group (n=35)	P values
Age (Mean ± SD) (years)	61.7 ± 10.1	62.2 ± 10.9	0.86
Gender (Male) %	17 (51.5%)	20 (57.1%)	0.65
Education status (literate) %	16 (48.5%)	23 (65.7%)	0.16
Occupation:			
Employed	10 (30.3%)	10 (28.6%)	0.05
Self Employed	4 (12.1%)	5 (14.3%)	
Farming	2 (6.1%)	11 (31.4%)	
House Keeper	13 (39.4%)	8 (22.9%)	
Retired	4 (12.1%)	1 (2.9%)	

Urban	10 (30.3%)	6 (17.1%)	0.21
Rural	23 (69.7%)	29 (82.9%)	
Risk Factor status:			
Smoking Status:			
Never smoked (yes)	10 (30.3%)	9 (25.7%)	0.40
Ex-smoker (yes)	17 (51.5%)	23 (65.7%)	
Current smoker (yes)	6 (18.2%)	3 (8.6%)	
Smoking Index (Mean ± SD)	394.88 ± 481.27	422.45 ± 578.21	0.83
Smoke	23 (69.7%)	26 (74.3%)	0.68
Biomass fuel smoke exposure (yes)	33 (100%)	33 (94.3%)	0.17
Frequency of exposure:			
Occasionally	14 (42.4%)	13 (37.1%)	0.89
Frequently	15 (45.5%)	18 (51.4%)	
Daily	4 (12.1%)	4 (11.4%)	
Duration of Biomass fuel smoke exposure (years)	33 (49.70 ± 9.76)	35 (44.89 ± 16.65)	0.15
NYHA Class (Mean ± SD)	2.33 ± 0.48	2.43 ± 0.61	0.48
HR at rest	88.67 ± 8.14	90.34 ± 10.34	0.31
HR after 6MWT	98.55 ± 9.44	100.63 ± 12.07	0.43
Dyspnea Borg score at rest	1.79 ± 0.48	1.89 ± 0.75	0.06
Dyspnea Borg score after 6MWT	3.48 ± 1.09	4.03 ± 1.27	0.75
Fatigue Borg score at rest	1.79 ± 0.5	1.83 ± 0.5	0.75
Fatigue Borg score after 6MWT	3.45 ± 1.1	3.86 ± 1.0	0.12
SPO_2 at rest	88.76 ± 1.7	88.37 ± 1.8	0.37
SPO_2 after 6MWT	80.64 ± 2.8	79.14 ± 5.0	0.14
Change in SPO2	-8.12 ± 2.2	-9.23 ± 4.3	0.19
6-minute walk distance (meters)	296.1 ± 55.3	290.7 ± 54.4	0.69
Stopped before 6MWT (%)	12 (36.4%)	17 (48.6%)	0.32
Symptoms score	33.69 ± 16.98	33.40 ± 16.48	0.94
Activity score	75.88 ± 14.52	83.27 ± 16.66	0.06
Impact score	43.28 ± 12.82	47.20 ± 13.14	0.22
Total score	51.57 ± 11.39	55.84 ± 12.08	0.14
SVC(%predicted)	52.27 ± 10.31	52.73 ± 13.05	0.87
FVC(%predicted)	45.12 ± 12.07	46.79 ± 14.27	0.60
FEV_1(%predicted)	42.05 ± 15.17	42.63 ± 16.73	0.88
$FEF_{25-75\%}$(%predicted)	18.78 ± 14.48	17.78 ± 7.30	0.72
FEV_1/FVC(%predicted)	73.07 ± 13.11	71.81 ± 10.85	0.67
Hb (gm/dl)	14.89 ± 1.41	14.93 ± 1.81	0.92
BUN (mg/dl)	40.17 ± 12.25	38.82 ± 12.19	0.65
Creatinine (mg/dl)	1.09 ± 0.15	1.08 ± 0.17	0.67
Medications:			

Theophylline group OD	16 (48.5%)	25 (71.4%)	0.05
LABA+ Corticosteroids OD	22 (66.7%)	27 (77.1%)	0.34
Anticholinergics OD	24 (72.7%)	28 (80.0%)	0.48
Anticholinergics+ Corticosteroids OD	5 (15.2%)	7 (20.0%)	0.60
Domiciliary O_2 therapy	6 (18.2%)	12 (34.3%)	0.13

Table 1: *Clinical characteristics of the study groups.*

Effect of Tadalafil on Cardiopulmonary Hemodynamics

Effort Tolerance:

a. Tadalafil resulted in significant increase in 6-minute walk distance, (336.7 ± 63.0 meters versus 290.7 ± 54.3 meters, $p < 0.001$).
b. The mean NYHA functional class decreased but was statistically not significant (2.3 ± 0.5 versus 2.4 ± 0.6, $p > 0.29$).
c. The dyspnea and fatigue Borg score decreased significantly (2.9 ± 1.1 versus 4.0 ± 1.2, $p < 0.005$), and (2.8 ± 1.1 versus 3.8 ± 1.0, $p < 0.005$), respectively.
d. Proportion of patients needing rest during 6-minute walk test was decreased (37.1% versus 48.6%, $p > 0.35$).
e. Tadalafil increased the arterial oxygen saturation at rest and during peak of 6-minute walk test (90.9 ± 1.7% versus 88.3 ± 1.7%, $p < 0.0000$), and (83.8 ± 4.5% versus 79.1 ± 5.0%, $p < 0.0000$), respectively.
f. The exercise induced decrease in arterial oxygen saturation was significantly less in tadalafil group (7.0 ± 3.1% versus 9.2 ± 4.3%, $p < 0.002$) significantly.

Quality of Life: The indices of quality of life were also significantly improved in tadalafil group:

a. The mean Activity score (64.4 ± 8.5 versus 83.2 ± 16.6, $p < 0.0000$), Impact score (36.2 ± 10.8 versus 47.2 ± 13.1, $p < 0.003$), and the Total score (44.3 ± 9.0 versus 55.8 ± 12.0, $p < 0.0004$).

Indices of RV Function: Tadalafil improved indices of RV systolic Function significantly;increased pulmonary flow velocity time integral (PFVTI) (14.54 ± 3.17 cm versus 12.25 ± 2.25 cm, $p < 0.0002$), increased tricuspid annular plane systolic excursion (TAPSE) (18.53 ± 4.0 mm versus 17.11 ± 3.94 mm, $p < 0.002$), improved RVFS 30.6 ± 8.2% vs. 24.8 ± 7.4% $p<0.002$, improved right ventricular eccentricity index in systole (1.05 ± 0.01 versus 1.06 ± 0.01, $p < 0.007$) and in diastole (1.05 ± 0.01 versus 1.06 ± 0.01, $p < 0.001$), significantly.

Pulmonary Haemodynamics: Tadalafil did not result in significant change in TR gradient (56.7 ± 3.2 vs. 55.2 ± 10.1). However, pulmonary flow acceleration time (PFAT) increased significantly (89.8 ± 11.7 vs. 76.2 ± 8.2 $p < 0.001$). There was a trend of decrease in PVR but was statistically not significant (3.1 ± 1.0 vs. 3.6 ± 0.9).

Pulmonary Functions: The tadalafil group also had significantly better indices of pulmonary functions compare to control group; SVC, FVC, FEV_1 and $FEF_{25-75\%}$ (63.4 ± 12.0 versus 52.7 ± 13.0, $p < 0.0003$), (58.0 ± 14.3 versus 46.7 ± 14.2, $p < 0.0001$), (56.4 ± 15.4 versus 42.6 ± 16.7, $p < 0.0001$), and (24.3 ± 8.9 versus 17.7 ± 7.3, $p < 0.0001$), respectively. (Table-2)

Characteristics	Control group (n = 33)	Intervention group (n = 35)	Mean difference (95% C.I.)	P value
NYHA Class	2.45 ± 0.51	2.31 ± 0.58	0.14 (-0.12 to 0.40)	0.29
HR at rest	90.42 ± 8.81	83.63 ± 10.40	6.80 (2.12 to 11.48)	0.005
HR after 6MWT	101.39 ± 11.56	91.46 ± 12.37	9.94 (4.13 to 15.74)	0.001
Dyspnea Borg score at rest	1.91 ± 0.58	1.66 ± 0.73	0.25 (-0.07 to 0.57)	0.12
Dyspnea Borg score after 6MWT	3.91 ± 1.49	2.91 ± 1.15	1.00 (0.35 to 1.64)	0.005
Fatigue Borg score at rest	1.91 ± 0.58	1.71 ± 0.68	0.25 (-0.07 to 0.57)	0.19
Fatigue Borg score after 6MWT	3.88 ± 1.47	2.87 ± 1.13	1.01 (0.37 to 1.64)	0.005
SPO2 at rest	87.91 ± 2.17	90.94 ± 1.75	-3.03 (-3.99 to -2.08)	0.0000
SPO2 after 6MWT	78.55 ± 4.92	83.89 ± 4.56	-5.34 (-7.63 to -3.05)	0.0000
Change in SPO2	-9.36 ± 3.37	-7.06 ± 3.19	-2.31 (0.72 to 3.90)	0.002
6-minute walk distance	285.45 ± 65.63	336.71 ± 63.05	-51.26 (-82.42 to -20.11)	0.001
Stopped before 6MWT (%)	16 (48.5%)	13 (37.1%)	0.63 (Odds Ratio)	0.35
Symptoms score	34.30 ± 16.99	33.40 ± 16.48	8.98 (-7.21 to 9.01)	0.83
Activity score	78.25 ± 14.14	64.40 ± 8.53	13.85 (8.23 to 19.47)	0.0000
Impact score	47.04 ± 15.77	36.25 ± 10.85	1.08 (4.27 to 1.73)	0.003
Total score	54.38 ± 12.93	44.31 ± 9.04	1.01 (4.70 to 1.55)	0.0004
SVC (%predicted)	53.84 ± 9.78	63.49 ± 12.05	-9.66 (-14.99 to -4.32)	0.0003
FVC (%predicted)	45.13 ± 10.56	58.06 ± 14.39	-12.94 (-19.08 to -6.80)	0.0001
FEV1 (%predicted)	41.21 ± 12.70	56.47 ± 15.47	-15.26 (-22.14 to -8.38)	0.0001
FEF25-75% (%predicted)	18.55 ± 13.85	24.31 ± 8.98	-5.76 (-11.38 to -0.14)	0.0001
FEV1/FVC (%predicted)	73.65 ± 14.02	77.45 ± 9.38	-3.80 (-9.63 to 2.04)	0.19
Hb (gm/dl)	14.87 ± 1.36	14.98 ± 1.76	-0.12 (-0.87 to 0.64)	0.76
BUN (mg/dl)	44.02 ± 15.57	33.33 ± 6.98	10.69 (4.91 to 16.74)	0.0006
Creatinine (mg/dl)	1.12 ± 0.16	1.02 ± 0.11	0.10 (0.04 to 0.17)	0.001
Medications:				
Theophylline group OD	18 (54.5%)	23 (65.7%)	-0.11 (-0.35 to 0.12)	0.35
LABA+ Corticosteroids OD	26 (78.8%)	28 (80.0%)	-0.01 (-0.21 to 0.18)	0.90
Anticholinergics OD	25 (75.8%)	27 (77.1%)	-0.01 (-0.22 to 0.19)	0.89
Anticholinergics+ Corticosteroids OD	6 (18.2%)	6 (17.1%)	-0.17 (-0.21 to 0.19)	0.91
Domiciliary O_2 therapy	8 (24.2%)	14 (40%)	-0.15 (-0.38 to 0.06)	0.17

Table 2: *Effects of tadalafil on exercise capacity and quality of life.*

Discussion: The effect of tadalafil on exercise capacity and quality of life was assessed in patients of chronic pulmonary disease with PH. Tadalafil improved the exercise capacity and quality of life significantly. The resting and post 6-minute walk arterial oxygen saturation also increased significantly with tadalafil. Improvement in exercise capacity was also reported by other investigators [11-20]. The underlying mechanisms of improved exercise capacity and quality of life with tadalafil in the patient population studied could be mediated by improvement in cardiopulmonary haemodynamics by lowering PVR thus improvement in exercise induced increase in cardiac output. This is also supported by the observation that the resting and exercise induced arterial oxygen saturation was significantly

higher and the BUN and serum creatinine had decreased significantly in the intervention group. The improvement in arterial saturation may also be mediated by improvement in ventilation-perfusion matching mediated by tadalafil by vasodilatation of pulmonary arterioles perfusing better ventilated alveoli [21,22]. The improvement of glomerular filtration with tadalafil apart from improved cardiopulmonary haemodynamic effects could also be mediated by vasodilatory effect of tadalafil on renal vascular bed [23-30]. Comparison of pulmonary functions between intervention and control group reveal significant improvement in the tadalafil group. However, the significant improvements in pulmonary function tests cannot be due to the tadalafil alone as patients were also advised to take inhaled bronchodilators also both long term and short term on regular basis depending on patient's condition. The tadalafil has been reported to have vascular smooth muscle relaxation effect on bronchial smooth muscles [31-35]. Thus the improvement in exercise capacity and quality of life with tadalafil in patients of chronic pulmonary disease may be mediated by diverse mechanisms.

Limitations: It was a pilot study. Number of subjects was small due to low prevalence of PH. Study subjects were not truly inhabitants of high altitudes thus the efficacy of tadalafil in patients of chronic pulmonary disease residing at high altitude with hypobaric hypoxia cannot be ascertained from the present study. It was not a placebo controlled double blind study thus the element of measurement bias and placebo effect cannot be ruled out.

Conclusion: In the present study, tadalafil 40 mg once daily showed significant improvement in the exercise capacity and in quality of life in patients with chronic pulmonary diseases with PH.

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