ORIGINAL ARTICLE

EFFECTS OF TADALAFIL ON CARDIOPULMONARY HAEMODYNAMICS IN PATIENTS OF CHRONIC PULMONARY DISEASES WITH PULMONARY HYPERTENSION: A PILOT STUDY

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ABSTRACT

Background and Objectives: Effect of tadalafil on cardiopulmonary haemodynamics in patients of chronic pulmonary diseases residing at an altitude has not been studied adequately. The present study reports the effect of tadalafil on cardiopulmonary haemodynamics in patients of chronic pulmonary diseases with PH residing at an altitude ranging between 1000 meters to 2500 meters above mean sea level.

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. The effect of tadalafil on cardiopulmonary haemodynamics was assessed after 3 months of tadalafil exposure. The echo Doppler derived indices of cardiopulmonary haemodymics recorded were; TR gradient, pulmonary flow acceleration time, pulmonary vascular resistance, myocardial performance index, RV eccentricity index, tricuspid annular plane systolic excursion and cardiac output. The arterial oxygen saturation was measured by Pulse oxymeter.

Results and Interpretation: Tadalafil significantly improved the indices of RV performance; pulmonary flow velocity time integral (14.54 ± 3.17cm versus 12.25 ± 2.25cm, $p < 0.0002$), tricuspid annular plane systolic excursion (18.53±4.0mm versus 17.11±3.94mm, $p<0.002$), RVFS 30.6% vs. 24.8% $p<0.003$. There was no significant change in the TR gradient although PFAT increased significantly with tadalafil; (89.8±11.7 vs. 76.2±8.2 msec. $p<0.001$). There was a trend of lower PVR with tadalafil buts not statistically significant 3.6±0.9 vs. 3.1±1.0. Tadalafil also improved the arterial oxygen saturation, SPO_2 (90.91±1.76% versus 88.40±1.79%, $p<0.0001$) significantly.

Conclusions: Tadalafil improved RV function significantly but its effect on PVR was modest.

Key words: Cardiopulmonary haemodynamics**,** Phosphodiesterase-5 inhibitors, Pulmonary hypertension, Tadalafil.

Trial registration: CTRI/2015/01/005413.

INTRODUCTION

Pulmonary hypertension (PH), a condition of elevated pressure in the pulmonary vasculature, is a common co-morbidity observed in the setting of parenchymal lung disease and in patients who experience chronic hypoxemia.[1] Amongst chronic lung diseases, PH occurs frequently in patients with chronic obstructive lung disease (COPD) as well as in patients with interstitial lung disease (ILD).[2] COPD is a leading cause of morbidity and mortality with WHO's Global Burden of Disease and Risk Factors project[3] showing that in 2001, COPD was the fifth leading cause of death in high-income countries, accounting for 3.8% of total deaths, and it was the sixth leading cause of death in nations of low and middle income, accounting for 4.9% of total deaths.[3] Interstitial lung diseases (ILDs), also known as diffuse parenchymal lung diseases (DPLDs) refers to a group of lung diseases affecting the interstitium (the tissue and space around the air sacs of the lungs). It concerns alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues. As the inflammation causes thickening and scarring of the interstitium, gas exchange at the alveolo-capillary membrane gets impaired and patient gradually becomes dyspneic even at rest.[4]

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[5] and/or Pulmonary flow acceleration time <90 msec[6-7] has been taken as an evidence of the presence of PAH. The sensitivity and specificity for the detection of PAH 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.[8] 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.[9] The response of PDE-5 inhibitors in the setting of low atmospheric tension among natives of medium altitude has not been reported. The present study reports the effect of tadalafil on the cardiopulmonary haemodynamics in patients of chronic pulmonary diseases with PH residing at an altitude of 1000 meters to 2500 meters above mean sea level.

METHODOLOGY

Study population and selection process: The patient population screened for recruitment to the study were all consecutive patients of chronic pulmonary diseases; chronic obstructive pulmonary diseases, interstitial lung diseases and post-tubercular pulmonary fibrosis attending the outpatient service of pulmonary medicine. Diagnosis of PH was based on the following criteria; TR gradient of ≥46 mmHg and/or pulmonary flow acceleration time of ≤90 msec.[5-7] Patients of stable chronic pulmonary disease with PH, aged between 20 to 80 years and willing to participate in the study after informed consent were enrolled. Patients were excluded if they had a history or clinical evidence of chronic pulmonary diseases with acute exacerbation and or 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 those already on tadalafil therapy.

Study design: It was a tertiary care centre hospital based Randomized controlled trial. Patients were recruited from July 2013 to July 2014 and follow up ended by Oct. 2014. The study protocol was approved by IGMC ethical committee.

Baseline data collection: Data pertaining to socio-demographic characteristics, exposure to self reported tobacco smoking and biomass fuel smoke was recorded using structured questionnaires. The status of effort tolerance using NYHA functional class was recorded. The medications prescribed for chronic lung disease by treating physician was also recorded. Examination included recording of blood pressure, heart rate, and arterial oxygen saturation with pulse oxymeter model: DR-50D. Severity of pulmonary function compromise was assessed by measuring the lung volumes and flow rates using spirometer model Vitalgraph-Compact-Buckingham, England.

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 following indices of cardiopulmonary hemodynamic parameters:

- Indices of RV systolic Function;

  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 RVOT to end of the spectral envelop.

- Pulmonary flow acceleration time (PFAT); Time interval from beginning of the pulse Doppler signal to the peak of spectral envelop at RVOT.

- 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 PAP.

- PVR was estimated by recording velocity time integral (VTI) of pulse Doppler spectral recorded in RVOT and maximum TR velocity (TRV max)measured by using colour flow mapping guided Continuous wave TR Doppler signal and using the formula (TR Vmax/RVOT VTI)×10 + 0.16.

- 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.

- 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.

- 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 chor-

dae, divided to minor-axis perpendicular to and bisecting the septum at the same section.

After baseline evaluation patients were randomized to tadalafil or control group using stratified randomization method. Patients were stratified based on gender and age groups of 10 years age interval.

Randomization procedure: The envelope was opened after patient's eligibility was confirmed and informed consent was obtained. Under each strata, envelope containing equal number of opaque sealed envelopes bearing treatment codes were numbered sequentially so that order of treatment allocation codes was random. The treatment allocation was concealed and investigator assigning was not participating in patient evaluation and outcome measurement. Treatment group was assigned by picking up first number in the sequentially numbered sealed opaque envelop from the respective strata the patient belonged to.

Intervention; Patients randomized to tadalafil group received tadalafil 40 mg once a day apart from usual care prescribed by the treating physician. In the control group patients received usual therapy as per patient's underlying chronic lung disease.

Follow up Period: All the patients were examined 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.

Outcomes measured: At the end of three months all patients underwent repeat echo Doppler evaluation for recording of indices of cardiopulmonary haemodynamics as at baseline. Investigator measuring the outcome was blinded to the 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 between 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 analysed using Epi Info version 3.4.3.

Trial registration: Central trial registry of India: CTRI/2015/01/005413.

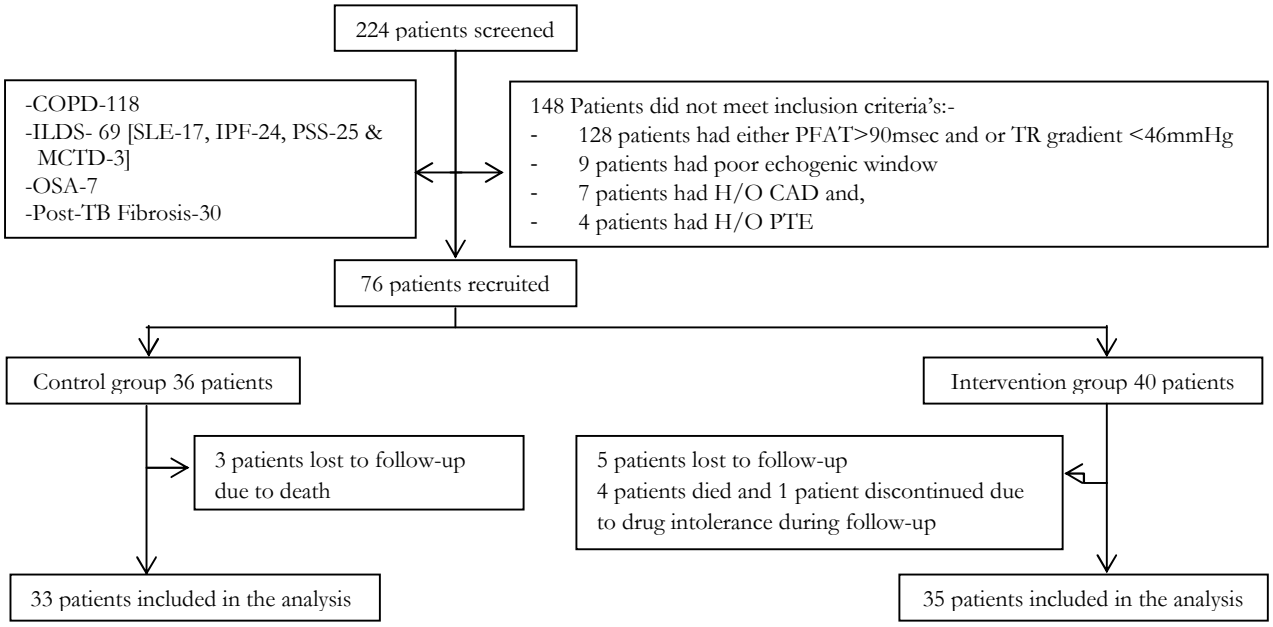

Fig 1: Flow chart of patients screened, enrolled, randomized and followed up.

RESULTS

Baseline clinical characteristics of the study groups: Table 1 describes the distribution of clinical characteristics of the study population under intervention and control arm; in brief. Both the study groups were well matched for socio demographical and geographical characteristics, exposure to tobacco smoke and biomass fuel smoke, NYHA functional class, resting SPO_2, and SPO_2 at peak of 6-MWT. The baseline distribution of indicators of pulmonary hemodynamic status; TR gradient, PFAT, RVOT VTI, PVR, and indices of RV functions; MPI, TAPSE, RVFS% and RV eccentricity index was also well matched. The indices of pulmonary functions were also similar between the groups. The mean Hb levels and renal functions were also well matched. The medications used and use of domiciliary oxygen therapy was also similarly distributed in both the groups.

Table 1: Clinical characteristics of the study groups

Characteristics	Group-A (%) (n=35)	Group-B (%) (n=33)	P values
Age (Mean ± SD) (years)	62.2 ± 10.9	61.7 ± 10.1	0.86
Gender (Male) %	20 (57.1)	17 (51.5)	0.65
Education status (literate) %	23 (65.7)	16 (48.5)	0.16
Occupation			
Employed	10 (28.6)	10 (30.3)	0.05
Self Employed	5 (14.3)	4 (12.1)	
Farming	11 (31.4)	2 (6.1)	
House Keeper	8 (22.9)	13 (39.4)	
Retired	1 (2.9)	4 (12.1)	
Residence			
Urban	6 (17.1)	10 (30.3)	0.21
Rural	29 (82.9)	23 (69.7)	
Smoking Status			
Never smoked (yes)	9 (25.7)	10 (30.3)	0.40
Ex-smoker (yes)	23 (65.7)	17 (51.5)	
Current smoker (yes)	3 (8.6)	6 (18.2)	
Smoking Index (Mean ± SD)	422.45 ± 578.21	394.88 ± 481.27	0.83
Smoke	26 (74.3)	23 (69.7)	0.68
Biomass fuel smoke exposure (yes)	33 (94.3)	33 (100)	0.17
Frequency of exposure			
Occasionally	13 (37.1)	14 (42.4)	0.89
Frequently	18 (51.4)	15 (45.5)	
Daily	4 (11.4)	4 (12.1)	
Duration of Biomass fuel smoke exposure (years)	35 (44.89 ± 16.65)	33 (49.70 ± 9.76)	0.15

Table 2: Baseline cardiopulmonary haemodynamic parameters, pulmonary function test variables, biochemical investigations and medications

Characteristics	Group-A (%) (n=35)	Group-B (%) (n=33)	P values
NYHA Class (Mean ± SD)	2.33 ± 0.48	2.43 ± 0.61	0.48
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
TR grad. (mmHg)	11 (53.05 ± 10.55)	14 (60.24 ± 19.17)	0.28
PFAT (msec)	77.75 ± 5.25	73.71 ± 9.29	0.11
PFVTI (cm)	11.92 ± 2.41	12.78 ± 2.91	0.19
PVR (woods unit)	11(3.76 ±1.49)	11(3.78 ± 1.66)	0.98
MPI	0.32 ± 0.19	0.35 ± 0.22	0.54
TAPSE (mm)	15.76 ± 2.15	17.11 ± 3.94	0.09
RVFS (%)	24.21 ± 7.09	30.17 ± 8.32	0.003
RV Eccentricity Index (Systole)	1.06 ± 0.02	1.06 ± 0.01	0.77
RV Eccentricity Index (Diastole)	1.06 ± 0.01	1.06 ± 0.01	0.37
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:			
Methylxanthines 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+ LABA OD	5(15.2)	7(20.0)	0.60
Domiciliary O_2 therapy	6(18.2)	12(34.3)	0.13

Table 3: Effects of tadalafil on the cardiopulmonary haemodynamic status

Characteristics	Group-A (n=35)	Group-B (n=33)	Mean difference(95% CI)	P value
NYHA Class	2.31 ± 0.58	2.45 ± 0.51	0.14(-0.12 to 0.40)	0.29
SPO_2 at rest	90.94 ± 1.75	87.91 ± 2.17	-3.03(-3.99 to -2.08)	0.0000
SPO_2 after 6MWT	83.89 ± 4.56	78.55 ± 4.92	-5.34(-7.63 to -3.05)	0.0000
TR grad. (mmHg)	14 (56.70 ± 13.27)	11 (55.22 ± 10.14)	-1.48(-11.17 to 8.21)	0.76
PFAT (msec)	89.87 ± 11.70	76.29 ± 8.21	-13.58(-18.50 to -8.65)	0.0000
PFVTI (cm)	14.54 ± 3.17	12.25 ± 2.25	-2.29 (-3.62 to -0.95)	0.0002
PVR (woods unit)	14 (3.16 ± 1.08)	11 (3.64 ± 0.93)	0.49(-0.35 to 1.32)	0.24
MPI	0.33 ± 0.20	0.33 ± 0.18	-0.01(-0.10 to 0.09)	0.89
TAPSE (mm)	18.53 ± 4.0	15.96 ± 2.90	-2.57(-4.27 to -0.87)	0.002
RVFS (%)	30.60 ± 8.21	24.82 ± 7.48	-5.78(-9.59 to -1.97)	0.003
RV Eccentricity Index (Systole)	1.05 ± 0.01	1.06 ± 0.01	0.01(0.00 to 0.01)	0.007
RV Eccentricity Index (Diastole)	1.05 ± 0.01	1.06 ± 0.01	0.01(0.00 to 0.02)	0.001
SVC(%predicted)	63.49 ± 12.05	53.84 ± 9.78	-9.66(-14.99 to -4.32)	0.0003
FVC(%predicted)	58.06 ± 14.39	45.13 ± 10.56	-12.94(-19.08 to -6.80)	0.0001
FEV_1(%predicted)	56.47 ± 15.47	41.21 ± 12.70	-15.26(-22.14 to -8.38)	0.0001
$FEF_{25-75\%}$(%predicted)	24.31 ± 8.98	18.55 ± 13.85	-5.76(-11.38 to -0.14)	0.0001
FEV_1/FVC(%predicted)	77.45 ± 9.38	73.65 ± 14.02	-3.80(-9.63 to 2.04)	0.19
Hb(gm/dl)	14.98 ± 1.76	14.87 ± 1.36	-0.12(-0.87 to 0.64)	0.76
BUN(mg/dl)	33.33 ± 6.98	44.02 ± 15.57	10.69(4.91 to 16.74)	0.0006
Creatinine(mg/dl)	1.02 ± 0.11	1.12 ± 0.16	0.10(0.04 to 0.17)	0.001
Medications:				
Methylxanthines group OD	23(65.7%)	18(54.5%)	-0.11(-0.35 to 0.12)	0.35
LABA+ Corticosteroids OD	28(80.0%)	26(78.8%)	-0.01(-0.21 to 0.18)	0.90
Anticholinergics OD	27(77.1%)	25(75.8%)	-0.01(-0.22 to 0.19)	0.89
Anticholinergics+ Corticosteroids OD	6(17.1%)	6(18.2%)	-0.17(-0.21 to 0.19)	0.91
Domiciliary O2 therapy	14(40%)	8(24.2%)	-0.15(-0.38 to 0.06)	0.17

Effect of Tadalafil on Cardiopulmonary Hemodynamics:

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 Hemodynamics; 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; (Table 2) It was intriguing that the all the indices of pulmonary functions; FVC, FEV_1 and ratio of FEV_1/FVC were significantly improved in the tadalafil group.

Effort Tolerance; NYHA Class; There was no significant change in the functional class with tadalafil (2.3±.5 vs. 2.4±0.5). Resting SPO2; Tadalafil increased resting SPO2 and post 6-Minute walk test significantly.

Renal functions; Blood urea and serum Creatinine levels were significantly reduced by tadalafil.

DISCUSSION

The effect of tadalafil on cardiopulmonary haemodynamics was assessed in patients of chronic pulmonary disease with PH residing at altitude of 1000 to 2500 meter from sea level. Tadalafil improved the RV systolic function significantly as demonstrated by significant increase in TAPSE, RVFS%, RVOT VTI, and improvement in renal function. This improvement in RV systolic function is possibly mediated by decrease in PVR. Although tadalafil decreased the PVR (mean difference of 0.48 woods with 95% C.I. of -0.35 to 1.32) woods unit but was statistically not significant. Wide confidence interval of the mean change in PVR indicates the limited power of the study to detect the true change in PVR with tadalafil due to small sample size. There was no significant decrease in TR gradient as the indicator of change in

PA systolic pressure (PASP). The failure to decrease in PASP with tadalafil may be related to proportionate increase in RV output. The usual treatment prescribed to the intervention and control group was as per the discretion of the treating physicians. There were no significant differences in the medications prescribed between the groups. Tadalafil may produce relaxation of the airway smooth muscle also leading to airway dilatation and improving the ventilator function. The significant increase in SPO_2 by tadalafil observed may be due to improvement in pulmonary function and RV output.[9-11]

The improvement of glomerular filtration with tadalafil apart from improved cardiopulmonary haemodynamic effects could also be due to the vasodilatory effect of tadalafil on the renal vascular bed. Tadalafil, as other PDE5 inhibitors, prevents the breakdown of NO derived cGMP, primarily in vascular smooth muscle cells, thus inducing vasodilator effects. It was observed in a study done on rats that at the renal level, PDE5 is localized to the vasculature, glomeruli, mesangial cells, cortical tubules, and inner medullary collecting duct cells of rat kidney, where its inhibition positively affects renal haemodynamic and excretory function.[12] The vasodilatory action of tadalafil is of a special importance in light of the intrarenal activation of vasoconstrictory systems that contribute to reduction in GFR, together with vascular congestion in the outer medulla and activation of tubule-glomerular feedback.[13] The improvement in arterial saturation may also be mediated by an improvement in the ventilation-perfusion matching caused by tadalafil through vasodilatation of pulmonary arterioles perfusing better ventilated alveoli.[14]

Tadalafil has been reported to have vascular smooth muscle relaxation effect on bronchial smooth muscles isoenzyme-selective PDE inhibitors that have been known to cause bronchodilation are usually related to PDE type-3 and PDE type-4 types, but recently PDE type-5 inhibitions also has been implicated in reversing bronchoconstriction. Therefore, it is possible that oral tadalafil therapy may improve airway functions by causing airway smooth muscle relaxation. Tadalafil is a selective inhibitorof cyclic-GMP specific PDE-5, which is the predominant enzyme that metabolizes cyclic-GMP. Thus by inhibiting its metabolism, cyclic-GMP levels are raised.[15-21] Another mechanism of improvement in indices of pulmonary function test is decrease in airway hyperreactivity and decrease in airway inflammation and mucus production. It is possible that oral tadalafil therapy may improve airway functions by causing airway smooth muscle relaxation. These results were supported by some studies.[21-22] 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 patients condition. Thus the improvement in cardiopulmonary haemodynamic status with tadalafil in patients of chronic pulmonary disease can be attributed to diverse mechanisms.

LIMITATIONS

It was a Pilot study. 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 40mg once daily showed significant improvement in the cardiopulmonary hemodynamic status in patients with chronic pulmonary diseases with PH.

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