

# Effect of doxycycline in patients of moderate to severe chronic obstructive pulmonary disease with stable symptoms

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**Abstract:**

**BACKGROUND:** The protease-antiprotease hypothesis proposes that inflammatory cells and oxidative stress in chronic obstructive pulmonary disease (COPD) produce increased levels of proteolytic enzymes (neutrophil elastase, matrix metalloproteinases [MMP]) which contribute to destruction of parenchyma resulting in progressive decline in forced expiratory volume in one second. Doxycycline, a tetracycline analogue, possesses anti-inflammatory properties and inhibits MMP enzymes.

**OBJECTIVES:** To assess the effect of 4 weeks doxycycline in a dose of 100 mg once a day in patients of moderate to severe COPD with stable symptoms.

**METHODS:** In an interventional, randomized, observer-masked, parallel study design, the effect of doxycycline (100 mg once a day for 4 weeks) was assessed in patients of COPD having stable symptoms after a run-in period of 4 weeks. The study participants in reference group did not receive doxycycline. The parameters were pulmonary functions, systemic inflammation marker C-reactive protein (CRP), and medical research council (MRC) dyspnea scale. Use of systemic corticosteroids or antimicrobial agents was not allowed during the study period.

**RESULTS:** A total of 61 patients completed the study (31 patients in doxycycline group and 30 patients in reference group). At 4 weeks, the pulmonary functions significantly improved in doxycycline group and the mean reduction in baseline serum CRP was significantly greater in doxycycline group as compared with reference group. There was no significant improvement in MRC dyspnea scale in both groups at 4 weeks.

**CONCLUSION:** The anti-inflammatory and MMP-inhibiting property of doxycycline might have contributed to the improvement of parameters in this study.

**Key words:**

Anti-inflammatory, C-reactive protein, doxycycline, dyspnea, matrix metalloproteinase, respiratory function tests

The airflow limitation in chronic obstructive pulmonary disease (COPD) is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.<sup>[1]</sup> Current management includes smoking cessation, bronchodilators, corticosteroids, and pulmonary rehabilitation. Smoking cessation is the only intervention in COPD that is associated with decreased progression of disease. The protease-antiprotease model proposes that inflammatory cells and oxidative stress in COPD result in increased levels of proteolytic enzymes (matrix metalloproteinases [MMP], neutrophil elastase) and decreased levels of antiproteases ( $\alpha$ -1-antitrypsin, tissue inhibitors of metalloproteinases [TIMP]) which result in destruction of lung parenchyma leading to progressive decline of forced expiratory volume in one second (FEV<sub>1</sub>).<sup>[2,3]</sup> MMPs are zinc-dependent endopeptidases of which MMP-1, -2, -8, and -9 have shown major role in pathogenesis of COPD. The concentrations of MMP-1, -8, and -9 are increased in bronchoalveolar

lavage fluid from patients of COPD.<sup>[4,5]</sup>

Doxycycline, a tetracycline analogue, has shown to possess immunomodulatory properties in addition to its broad-spectrum antimicrobial activity. Doxycycline is a potent inhibitor of MMP enzymes, particularly MMP-8 and MMP-9.<sup>[6-9]</sup> Studies have demonstrated reduction of MMP-9 levels by doxycycline in lung tissues of rats.<sup>[10,11]</sup> Other immunomodulatory properties of doxycycline include suppression of neutrophil migration, antiapoptotic activity, decrease in monocyte chemoattractant protein-1, and increase in the expression/secretion of the natural inhibitor of MMP (TIMP-1).<sup>[12-14]</sup> Doxycycline has shown beneficial results in periodontitis, facial acne, recurrent oral ulceration, rheumatoid arthritis, and corneal erosions on account of its non-antimicrobial properties.<sup>[14-18]</sup> Long-term treatment with doxycycline is well tolerated. Adverse effects to doxycycline include photosensitivity and

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gastrointestinal disturbances.<sup>[19]</sup> It seemed reasonable to assume that drug possessing anti-inflammatory and MMP-inhibiting activity like doxycycline may have beneficial effect on lung function, systemic inflammation, and dyspnea in patients of COPD having stable symptoms. The present study was designed to study the effect of doxycycline in a dose of 100 mg once a day in patients of stable COPD.

## Methods

The study was conducted in the outpatient department of pulmonary medicine of M. P. Shah medical college and Guru gobindsingh government hospital, Gujarat, India. The study protocol was approved by the institutional ethics committee and designed in accordance with good clinical practice. Written informed consent was obtained from all the participants included in the study. The study was carried out between July 2009 and February 2010.

In the present study, an interventional, randomized, observer-masked, comparative design was used to investigate the efficacy of doxycycline in addition to standard treatment in patients of stable COPD. Patients included had age >40 years, smoking history >10 pack years, and were classified as stage II or III on GOLD classification for severity. Patients presenting with acute exacerbation of COPD as defined by Anthonisen *et al.*,<sup>[20]</sup> and patients who had moderate/severe exacerbation in last 4 weeks as defined by severity scale proposed by Cazzola *et al.*,<sup>[21]</sup> were excluded. Patients with active respiratory disease other than COPD (tuberculosis, pneumonia, lung malignancies, bronchial asthma), acute systemic/local infection, cardiac and gastrointestinal disorders were excluded. Patients on systemic corticosteroids at the time of screening were also excluded. The primary endpoint was change in post-bronchodilator FEV<sub>1</sub> from baseline to end of 4 weeks, and secondary endpoints were changes in forced expiratory volume (FVC), serum C-reactive protein (CRP), and medical research council (MRC) dyspnea scale after 4 weeks.

At initial screening visit, patients were assessed by history, clinical examination, pulmonary function tests, chest X-ray, and sputum examination. Data regarding smoking history and exacerbations were recorded. Patients who qualified inclusion and exclusion criteria and gave written informed consent underwent a run-in period of 4 weeks. During run-in period, all the study participants received treatment with deriphyllin (100 mg thrice a day), inhaled salbutamol and ipratropium. A run-in period of 4 weeks was selected because physiological changes associated with acute exacerbation return to baseline values in 70 to 74% patients at 4 weeks.<sup>[22]</sup> Use of inhaled corticosteroids and long-acting  $\beta_2$  agonists was allowed during the run-in and study period.

After run-in period, at baseline visit, patients were assessed for values of pulmonary functions by spirometry. Assessment of dyspnea was done using MRC dyspnea scale and blood sample was collected for serum CRP estimation. Subsequently, the study participants were randomized using blocked randomization method with the help of computer software into the following two groups: Group 1 (Doxycycline group): Capsule doxycycline 100 mg once a day daily for 4 weeks in addition to run-in period treatment; Group 2 (Reference group): Continued to receive treatment received in run-in period.

Systemic corticosteroids or antibiotics were not allowed during the study period until clinical necessity arose in which the patient was then excluded from the study.

After study intervention period of 4 weeks, patients were followed up and assessed for lung functions, MRC dyspnea scale, and serum CRP. Post-bronchodilator FEV<sub>1</sub> and FVC were recorded after administration of 200  $\mu$ g of salbutamol, using metered dose inhaler. Each subject performed a minimum three acceptable FVC measures. The greatest FEV<sub>1</sub> and corresponding FVC value were used in subsequent analysis. Serum CRP was estimated using immunoturbidimetry on the same day of collection of sample.

## Statistical analysis

A total of 36 patients were required in each group with the power of the study as 80% to detect a difference of 20% between the two groups in post-bronchodilator FEV<sub>1</sub> at 4 weeks. Baseline variables were compared using chi-square or Fisher's exact test for categorical variables and unpaired *t* test or Mann-Whitney test for continuous variables. Statistical evaluations were accomplished with paired *t* tests for before and after values of pulmonary functions for both groups and unpaired *t* test for difference in change among both groups. Change in serum CRP was expressed in percent change from baseline and compared using unpaired *t* test among both groups. Pre- and post-MRC dyspnea scores were compared using Wilcoxon signed rank test. *P* value <0.05 was considered as significant.

## Results

At baseline visit, 72 patients were randomized equally to two groups. During the study period, six patients were lost to follow-up and five received antibiotics/systemic corticosteroids on account of moderate to severe exacerbations. Thus, these 11 patients were excluded and data of remaining 61 patients were analyzed [Figure 1]. There was no significant difference in baseline variables of both groups at the end of run-in period [Table 1].

At baseline, there was a difference of 29 ml in the mean FEV<sub>1</sub> among two groups. At 4 weeks, mean FEV<sub>1</sub> increased significantly by 153 ml in doxycycline group (*P* < 0.001, 95%

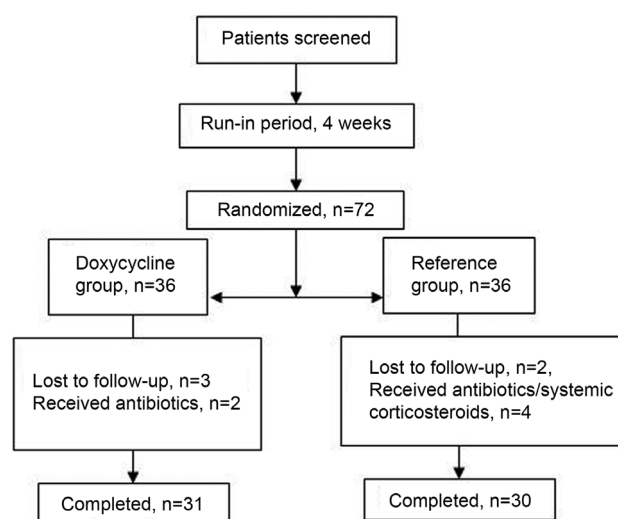


Figure 1: Trial profile

**Table 1: Baseline characteristics of study participants**

Baseline variable	Doxycycline group (n = 31)	Reference group (n = 30)	P value
Age, years	58.39 (8.58)	56.53 (11.29)	0.47
Smoking, pack-years*	30 (25-35)	20 (20-35)	0.3
BMI, kg/m <sup>2</sup>	17.57 (2.85)	18.46 (3.47)	0.27
Concomitant drugs, n (%)			
Theophylline	31 (100.0)	30 (100.0)	-
Salbutamol	31 (100.0)	30 (100.0)	-
Ipratropium	27 (87.1)	27 (90.0)	1.00
ICS	7 (22.6)	5 (16.7)	0.74
LABA	7 (22.6)	5 (16.7)	0.74
GOLD criteria, n			
II	8 (34.78)	8 (36.36)	0.93
III	23 (65.22)	22 (63.64)	0.93
Baseline FEV <sub>1</sub> , L	1.013 (0.29)	1.042 (0.24)	0.67
Baseline FEV <sub>1</sub> % predicted	42.81 (9.8)	42.98 (9.92)	0.94
Baseline FVC, L	1.614 (0.5)	1.740 (0.44)	0.30
Baseline FVC % predicted	54.99 (13.17)	58.95 (15.52)	0.28
Serum CRP, mg/l (n = 26)	10.68 (5.96)	8.03 (4.59)	0.07
MRC dyspnea scale*	4 (4-4)	4 (3-4)	0.67

Values expressed as mean (SD) unless specified, \*expressed as median (interquartile range). P value <0.05 considered significant. ICS = Inhaled corticosteroids; LABA = Long acting beta<sub>2</sub> agonists; MRC = Medical research council; CRP = C-reactive protein; FEV<sub>1</sub> = Forced expiratory volume in one second; FVC = Forced expiratory volume

CI = -0.190 to -0.116) and decreased by 33 ml in reference group [Table 2, Figure 2]. There was significant difference in the mean change in FEV<sub>1</sub> ( $\Delta$ FEV<sub>1</sub>) in both groups ( $P < 0.001$ , 95% CI = 0.140 to 0.234). There was significant increase in FEV<sub>1</sub>% predicted, FVC, and FVC % predicted from baseline values at 4 weeks in doxycycline group. Lung function parameters did not improve in reference group. There was significant difference in mean change in FEV<sub>1</sub>% predicted, FVC, and FVC % predicted among both groups. The mean percent reduction in baseline serum CRP was  $45.59 \pm 4.6$  and  $15.78 \pm 5.8$  in doxycycline and standard group, respectively. There was significant difference in reduction of serum CRP values between both groups. MRC dyspnea did not significantly decrease from baseline in both the groups at 4 weeks [Table 3].

## Discussion

Doxycycline in a dose of 100 mg once a day for duration of 7 to 10 days has been used as an antimicrobial agent to treat acute exacerbations in COPD. The present study is first of its kind in which efficacy of 4 weeks doxycycline was assessed in patients of stable COPD. All the study participants were male patients because of inclusion of only those patients who had smoking history of more than 10 pack-years and the fact that smoking is much less common in females in India. Both the groups were comparable in terms of drop-outs and withdrawals during the study period.

Doxycycline demonstrated improvement in lung function parameters for which antimicrobial action of doxycycline is unlikely to be responsible. The present study excluded patients with acute exacerbation, as defined by Anthonisen *et al.*<sup>[20]</sup> This classification indicates likelihood of bacterial

**Table 2: Change in pulmonary functions and serum CRP**

	Doxycycline group (n = 31)	Reference group (n = 30)	P value	95% CI
$\Delta$ FEV <sub>1</sub> , L	0.153 (0.01)	-0.033 (0.01)	<0.001	0.140-0.234
$\Delta$ FEV <sub>1</sub> % predicted	6.60 (0.88)	-1.39 (0.55)	<0.001	5.88-10.10
$\Delta$ FVC, L	0.162 (0.04)	-0.037 (0.04)	<0.005	0.076-0.324
$\Delta$ FVC % predicted	5.838 (1.72)	-1.513 (1.40)	<0.005	2.89-11.81
Serum CRP, % reduction	45.59 (4.6)	15.78 (5.8)	<0.001*	-

Values are mean (SE); P value by unpaired t test; \*P value by Mann-Whitney test; P value considered significant if <0.05. CRP = C-reactive protein; FEV<sub>1</sub> = Forced expiratory volume in one second; FVC = Forced expiratory volume

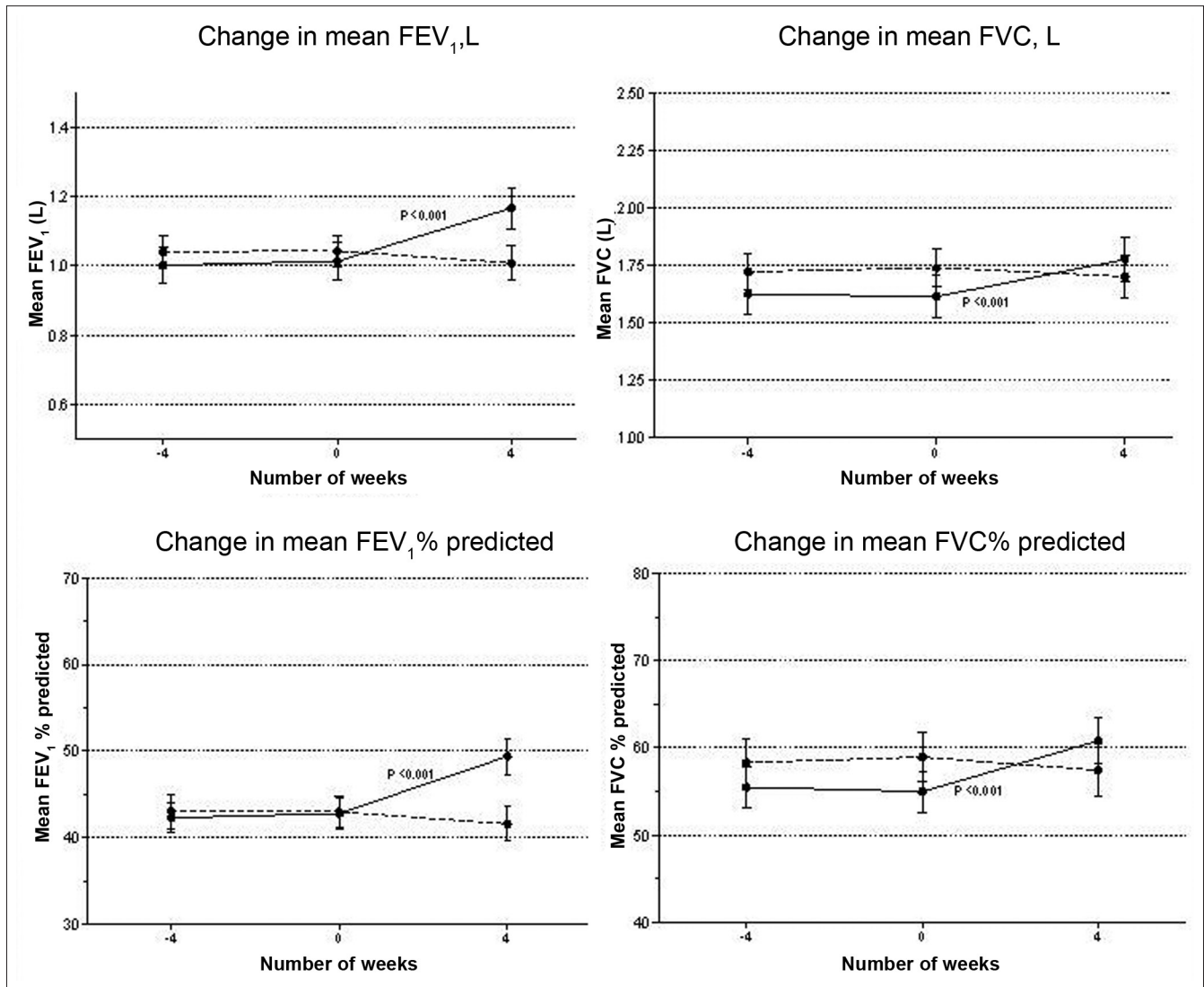
**Table 3: Change in MRC dyspnea scale**

Mean MRC scale	Doxycycline group (n = 31)	Standard group (n = 30)
Baseline	3.74 (0.51)	3.67 (0.61)
4 weeks	3.58 (0.67)	3.50 (0.62)
P value	0.072	0.072

Values are mean (SE); P value by Wilcoxon signed rank test. MRC = Medical research council

infection as cause of an exacerbation. The study also excluded patients who had moderate to severe exacerbations in last 4 weeks according to event-based definition given by Cazzola *et al.*<sup>[21]</sup> Patients having infective pathology were also excluded. A randomized controlled trial has provided evidence for significant beneficial effect of antibiotics only in those COPD patients who present with increase in all of the following cardinal symptoms: Dyspnea, increased sputum volume and sputum purulence<sup>[20]</sup> or who present with sputum purulence, and at least one of other two cardinal symptoms.<sup>[23]</sup> In conclusion, there is less possibility that antimicrobial action might have contributed to beneficial effect of doxycycline in improving lung function parameters in the present study.

Improvement in lung function parameters in present study might be the result of anti-inflammatory and MMP-inhibiting activity of doxycycline. A study demonstrated that the collagenase activity in tracheal aspirates from horses suffering from COPD was sensitive to doxycycline inhibition.<sup>[24]</sup> Study by Nordstrom *et al.*<sup>[14]</sup> tested clinical response to 3 months doxycycline in concert with collagenase activity in patients of rheumatoid arthritis. Significant reduction in joint score and pain visual analogue scale was seen as early as 6 weeks. In the same study, saliva samples showed significant reduction in collagenase (MMP-8) activity at 12 weeks. Doxycycline has shown improvement in pulmonary disorders in which dysregulated MMP activity is held responsible. Maugban *et al.*<sup>[25]</sup> studied the effect of addition of doxycycline to immunosuppressive therapy in lung transplantation patients with recurrent acute rejections or obliterative bronchiolitis (OB/BOS). This was associated with improved lung functions in serial pulmonary function tests. OB/BOS is associated with elevated MMP-9 levels and the immunomodulatory effect of doxycycline might have been responsible for the beneficial effect. Long treatment with



**Figure 2:** Change in mean pulmonary functions. Error bars represent SE. *P* value by paired *t* test for pre (baseline) and post (after 4 weeks) values. Straight line - doxycycline group, dotted line - reference group. Screening: -4 weeks, baseline: 0 week, post-intervention: 4 weeks

doxycycline in patient of idiopathic pulmonary fibrosis was associated with improvement in symptoms, physiological and radiological parameters.<sup>[26]</sup> Doxycycline inhibits neutrophil collagenase (MMP-8) and MMP-9 at doses readily attainable by therapeutic doses. It achieves similar concentration in lungs and plasma.<sup>[27,28]</sup>

Airway limitation and airway inflammation are separate and independent factors in pathophysiology of COPD. CRP reflects the total systemic burden of inflammation in patients of COPD.<sup>[29]</sup> Eight-year follow-up study of large cohort with airway obstruction showed that the increased CRP levels are strong predictor of COPD hospitalization and deaths<sup>[30]</sup> Increased serum CRP levels have been associated with all-cause mortality in patients with mild to moderate COPD, reduced lung function, and greater FEV<sub>1</sub> decline.<sup>[31]</sup> The present study demonstrated significant difference in reduction of baseline serum CRP levels in doxycycline and standard group. The baseline serum CRP was higher in doxycycline group, though this was not significant. Anti-inflammatory

agents like corticosteroids (inhaled fluticasone) for 2 weeks reduced baseline serum CRP levels by 50% in COPD patients who had stable symptoms in previous 3 months in a study.<sup>[32]</sup> In MIDAS trial, subantimicrobial doses of doxycycline significantly reduced serum CRP level by 47% in patients with coronary artery disease.<sup>[27]</sup> The study also demonstrated significant reduction in serum IL-6. The authors concluded that reduction in CRP due to doxycycline might be due to upstream inhibition of IL-6 or direct inhibitory effect on CRP synthesis in liver or both. IL-6 is a major signaling cytokine stimulant and induces CRP production and release by liver. Similar mechanism might be responsible for reduction in CRP in the present study.

Studies have demonstrated that dyspnea scores and lung function are distinct and separate in terms of their influence on health outcome.<sup>[33]</sup> The lack of improvement in MRC dyspnea scale despite significant increase in FEV<sub>1</sub> might be due to following reasons. First of all, the study intervention period might not be sufficiently long enough to change the



perceived respiratory disability in patients of stable COPD. Second, association of FEV<sub>1</sub> and MRC dyspnea scale has not been demonstrated.<sup>[34]</sup> Lastly, there could be factors other than COPD which might have contributed to dyspnea in the study participants.

Limitations of the study include short study intervention period and lack of data on effect of doxycycline on long-term clinical outcomes in COPD like symptom scores, health status, exercise tolerance, and exacerbation rates. Alternate explanation for serum CRP reduction in doxycycline group could be resolution of mild or occult infection which was not recognized prior to study. The study did not address the problem of antimicrobial resistance.

In conclusion, the study demonstrates beneficial effect of short-term doxycycline in lung function parameters and systemic inflammatory marker, CRP in patients of stable COPD.

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