Original Article

Pharmacological Management of Chronic Obstructive Pulmonary Disease by Low-Dose Theophylline: A Prospective Hospital-based Study in East Godavari of Andhra Pradesh

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Abstract

Background: High therapeutic dose of theophylline is not tolerated well by some patients. As it is an effective and affordable drug, the effectiveness of low-dose theophylline in pharmacological management of chronic obstructive pulmonary disease (COPD) was assessed. **Aim:** The aim of this study was to detect the efficacy of low-dose theophylline in COPD patients. **Patients and Methods:** Patients with stable COPD were enrolled. The complete blood picture (CBP), pulmonary function tests (PFTs), and St. George's Respiratory Questionnaire (SGRQ) were performed at enrolment. Patients were categorized into two groups: subjects and controls. All the participants were given medication for COPD as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. However, subjects were kept on low-dose sustained-release oral drug theophylline (150 mg twice daily) as an add-on. At every follow-up, once every 10 days up to 30 days, their parameters were recorded. The difference between the prognostic biomarkers was analyzed using the Student's "*t*"-test. **Results:** The CBP, SGRQ, and PFTs showed improvement in COPD patients treated with low-dose theophylline, i.e., subject group. Even though the PFTs improved in subjects, evidence of COPD remained. Low-dose theophylline may help to improve the quality of life in COPD patients. **Conclusion:** As a Cost-effective medication, low-dose theophylline can be used as an add-on drug to GOLD guidelines for the treatment of COPD. The subjects may feel better and can lead their normal life even with COPD.

Keywords: Complete blood picture, pulmonary disease, pulmonary function tests theophylline

Introduction

Theophylline, a xanthine derivative bronchodilator, has been used to treat chronic obstructive pulmonary disease (COPD) for over seven decades. Currently, it has lost popularity because of the introduction of more effective bronchodilators; theophylline is needed in relatively high concentrations (10–20 mg/L). At this high dose, theophylline can relax the human airway smooth muscle by elevating the cyclic adenosine monophosphate levels. Unfortunately, many patients are not able to tolerate high-dose therapeutic concentrations of theophylline. Current studies bring a new insight into the molecular action of low-dose sustained-release theophylline; it can reverse the steroid resistance in COPD and can act as anti-inflammatory drug.[1,2] Theophylline is recommended when other long-term bronchodilators are not available or patient cannot afford it.

A clinical diagnosis of COPD should be considered in patients having chronic cough, sputum production, and dyspnea and having a history of exposure to risk factors such as smoking or biomass fuel. The presence of postbronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio <0.7 confirms the diagnosis of COPD which remains a clinical diagnosis, confirmed by measurement of airflow limitation using spirometry, a postbronchodilator FEV_1 <80% (predicted). Although theophylline has effects when used in bronchodilator doses,

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increasing evidence shows that at low plasma concentrations, it has significant anti-inflammatory effects in COPD.[3]

Inhaled bronchodilators in COPD are central to symptom management and are commonly given on a regular basis to prevent or reduce symptoms. The aim of this study was to assess the effects of low-dose theophylline at 150 mg/day twice, added to long acting β2 agonist (LABA) + long-acting muscarinic antagonists (LAMAs) + inhaled corticosteroids (ICSs) rotahalers. This study was done in accordance with the provisions of the Declaration of Helsinki.

The primary goal of treatment was to improve exercise capacity, lung function, and to reduce symptoms of dyspnea. Secondary aims were to evaluate self-reported COPD symptoms and intake of relief medications and lung function variables such as Forced expiratory volume in 1 second (FEV1), Forced vital capacity(FVC).

Patients and Methods

We enrolled 472 COPD patients above 65 years of age, among 620 patients who presented to the pulmonology department of our hospital during the year 2016–2018. One hundred and forty-eight patients were excluded from this study due to a history of right heart failure, severe diabetes, hypertension, and not willing to continue in this study. After explaining the protocol and benefits of this in their own language, written informed consent was obtained from all the participants for participation in the study as well as presentation of the data for research purposes.

All the consenting patients were investigated for COPD through routine tests (1) chest X-ray, (2) complete blood picture (CBP), (3) sputum bacterial culture sensitivity, and (4) pulmonary function tests (PFTs). The diagnosis of COPD was obtained by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: The presence of a post-bronchodilator FEV1/FVC <0.70 confirms the presence of persistant airflow limitation. Most of the participants had at least one exacerbation in the past 6 months before screening. Mild-to-moderate COPD cases with exacerbations were enrolled in this study.

For the clinical and prognostic assessment of the patients, St. George's Respiratory Questionnaire (SGRQ) was used. This included assessment of the frequency of cough episodes, quantity of sputum/per day, baseline dyspnea index grading improvement, frequency of rotahalers use, and 6-min walk test (6MWD test).[4] CBP of the patients such as white cell count, neutrophils, eosinophils, monocytes, basophils, and erythrocyte sedimentation rate (ESR) was assessed. All the participants were from poor and lower middle-class background and most of them were daily Agricultural labourers and farmers. They were habituated to smoking cigars from a young age of 15 years.

Two hundred forty COPD patients were treated with 150 mg of theophylline, twice daily along with standard medication as per the GOLD guidelines, i.e., long-acting beta-2 agonists (LABA) + LAMA and ICSs rotahalers as the study group. Two hundred thirty-two participants were treated with only LABA + LAMA + ICS rotahalers and were considered as the control group.[5,6] Two hundred micrograms of budesonide, 6 μg of formoterol fumarate, and 80 μg of ipratropium bromide dry powder inhalers were used due to their cheap availability. Their effect lasted up to 24 h. Single-blind method was used in this study because the use of placebo was not acceptable to the institutional ethical committee.

During the 30 days of the study period, all the participants were followed up every 10 days, i.e., three times in a month. At every follow-up, CBP, SGRQ, and PFTs were obtained again. In each visit, the patients were examined with respect to the correctness of inhalation technique and were advised as appropriate. Cigar smoking was completely banned.

DxH 800 (Beckman Cell Counter, Inc., Brea, CA, USA) blood analyzer was used for CBP. Jaeger Master Screen spirometer (Jaeger, Inc., Bodnegg, Germany) was used for PFTs.

The data are presented as a mean ± standard deviation. Comparison of continuous variables between two groups was done using unpaired "*t*"-test. Statistical significance was accepted if $P < 0.05$. All the statistical analysis was done by GraphPad Insat 3 software.

Results

A total of 472 stable and eligible COPD patients underwent screening and enrolment to the study. The demographic and anthropometric characteristics of the patients and the use of respiratory medications were similar in both the study and control groups. The main characteristics of the subjects at the baseline are shown in Tables 1 and 2.

Table 1: Clinical and demographic characteristics of participants

Variable	Subjects (*n*=240)	Control (*n*=232)	*P*
Age (years)	66.5±5.6	65.5±5.8	0.2334
Gender (male/female)	169/71	152/80	-
Smoking (male/female)			
Yes	136/15	128/17	-
No	33/56	24/63	-
BMI (kg/m^2)	26.70±4.23	25.9±4.5	0.0766
CBP			
RBC (1×10^6/μL)	5.13±1.32	5.11±0.98	0.8524
WBC (1×10^3/μL)	6.33±1.98	6.13±1.24	0.1908
Neutrophils (1×10^3/μL)	5.42±1.09	5.63±1.98	0.1523
Lymphocyte (1×10^{10}/μL)	3.01±0.21	3.04±0.25	0.1582
Basophils (1×10/μL)	1.01±0.11	1.05±0.40	0.1364
Platelets (1×10^3/μL)	243.23±103.45	251.23±123.5	0.44449
Hb (g/dL)	14.43±5.12	14.83±4.22	0.3557
ESR (mm/h)	62.78±2.87	64.23±4.09	<0.0001

BMI: Body mass index, CBP: Complete blood picture, RBC: Red blood cell, WBC: While blood cell, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate

After all the three follow-ups, the overall comparison of variables between both the groups throughout the whole study was performed. In the study group, on the 10th day of posttreatment, the prognostic factors such as CBP, indices of SGRQ, and PFTs were significantly improved as compared to the control group except FVC % ($P = 0.0815$) [Tables 3 and 4].

On the 20th day of the examination, significant improvement from the baseline characteristics was seen among the subjects who were treated with theophylline along with the routine treatment. A significant decrease in sputum volume and increase of 6MWD were also seen. In CBP, we observed a significant decrease in neutrophils, eosinophils, and ESR. PFTs (FEV_1 and FEV_1/FVC ratio) showed significant improvement in the study group than control, while there was no significant difference with respect of FVC% ($P = 0.2164$).

All the subjects were instructed to come for follow-up on the 30th day of treatment and were assessed as before. All the parameters in CBP were significantly improved in the study group than in the control group. The study group showed subjective improvement as assessed by St. George's respiratory criteria. Sputum volume was lower in the study group with minimal cough episodes. Pulmonary functions also improved significantly in the study group [Figures 1 and 2].

Discussion

According to the GOLD guidelines 2019, controversy remains about the exact effects of xanthine derivatives. Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome p450 mixed-function oxidases. There is evidence for a modest bronchodilator effect compared with placebo in stable COPD. The addition of theophylline to salmeterol produces a greater improvement in FEV_1 and breathlessness than salmeterol alone.[7] The addition of theophylline to salmeterol produces a greater improvement in FEV_1 and breathlessness than salmeterol alone.[8] The GOLD 2018 and 2019 has recommended using the ABCD assessment tool for the treatment of COPD. However, GOLD 2019 has not included

Table 2: St. George's Respiratory Questionnaire and pulmonary function tests of the study participants

Variable SGRQ and PFT	Study group	Control group	*P*	Significant
Sputum volume (ml/day)	158.01±2.67	158.04±2.10	0.8924	Yes
MMRC dyspnea score	2.48±0.19	2.49±0.34	0.6646	Yes
6 MWD (m)	122.80±10.76	128.78±8.76	0.001	Yes
Number of cough episodes/day	15	14	-	
PFTs				
FVC % predicted	63.51±11.30	63.14±11.90	0.7296	Yes
FEV_1% predicted	60.42±8.10	60.97±7.41	0.4506	Yes
FEV_1/FVC % predicted	69.36±6.20	69.98±6.24	0.2798	Yes

SGRQ: St. George's Respiratory Questionnaire, PFTs: Pulmonary function tests, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, 6 MWD: 6-min walk distance, MMRC: Modified medical research council

Table 3: Overall comparison of complete blood picture between the control group and study group

CBP	Study versus/ control group	Pretreatment (*P*)	10th day treatment (*P*)	20th day treatment (*P*)	30th day treatment (*P*)
RBC (1×10^6 cells/μL)	Study group/ control group	5.31±1.32/5.76±0.45 (<0.001*)	5.30±1.02/5.56±0.12 (<0.001*)	5.12±2.25/5.12±1.21 (0.9991*)	5.21±0.24/5.62±0.34 (<0.0001*)
WBC (1×10^3 cells/μL)	Study group/ control group	6.33±1.98/6.24±1.23 (0.5549)	5.12±1.01/6.33±0.15 (<0.001*)	5.02±1.43/6.12±0.34 (<0.001*)	4.12±1.65/6.01±3.12 (<0.0001*)
Neutrophils (1×10^3 cells/μL)	Study group/ control group	5.42±1.09/5.45±0.12 (0.6770)	5.12±0.98/5.55±0.12 (<0.001*)	4.01±1.09/5.34±0.23 (<0.001*)	3.01±1.41/6.01±0.54 (<0.001*)
Lymphocytes (1×10^{10} cells/μL)	Study group/ control group	3.01±0.21/2.96±0.54 (0.1829)	2.67±0.45/2.96±0.12 (<0.001*)	2.61±0.21/3.01±0.02 (<0.0001*)	2.11±0.44/3.98±0.34 (<0.001*)
Basophils (1×10 cells/μL)	Study group/ control group	0.19±0.11/0.14±0.0.10 (<0.001*)	0.06±0.02/0.15±0.04 (<0.001*)	0.02±0.01/0.15±0.02 (<0.001*)	0.02±0.01/0.15±0.0.01 (<0.001*)
Eosinophils (1×10^2 cells/μL)	Study group/ control group	0.34±0.05/0.34±0.02 (0.9991)	0.29±0.03/0.32±0.11 (0.0001*)	0.28±0.05/0.34±0.10 (0.0001*)	0.11±0.01/0.34±0.05 (<0.0001*)
Platelets (1×10^3 cells/μL)	Study group/ control group	243.2±103.22/254.22±100.5 (0.2464)	216±98.13/243.12±95.12 (0.0024*)	218.44±121.23/212.09±114.23 (0.5586)	215.50±91.56/219.22±102.23 (0.6771)
Hb (g/dL)	Study group/ control group	14.43±5.12/14.83±4.22 (0.3357)	14.42±1.65/14.55±2.65 (0.5211)	13.89±2.09/13.22±2.98 (0.0048*)	13.98±0.89/14.00±1.09 (0.8270)
ESR (mm/h)	Study group/ control group	62.78±2.00/59.22±6.22 (0.0001*)	26.12±12.33/59.12±2.12 (<0.0001*)	25.54±11.23/64.94±1.33 (<0.0001*)	15.98±1.33/62.12±0.54 (<0.0001*)

**P* value. CBP: Complete blood picture, RBC: Red blood cell, WBC: While blood cell, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate

Table 4: Overall comparison of St. George's Respiratory Questionnaire and Pulmonary function tests between study group and control group

Days	Variable	Subject	Control	*P*
10th				
SGRQ	Sputum volume (ml/day)	105.12±2.67	121.23±3.11	0.0001
	Dyspnea	2.08±0.98	1.39±1.01	0.0008
	6 MWD test (m)	150.30±15.26	128.20±10.36	<0.0001
	Cough episodes/day	10	12	-
PFT	FVC % predicted	64.74±10.23	63.24±08.30	0.0815
	FEV_1% predicted	62.42±8.10	60.97±7.41	0.0432
	FEV_1/FVC % predicted	69.67±6.40	68.23±3.90	0.0034
20th				
SGRQ	Sputum volume (ml/day)	27.32±0.67	89.13±3.0	0.001
	Dyspnea	2.98±0.98	1.79±0.34	0.1862
	6 MWD test (m)	160.22±10.12	158.00±2.67	<0.0013
	Cough episodes/day	5	8	-
PFT	FVC % predicted	64.92±7.32	63.98±09.11	0.2164
	FEV_1% predicted	63.13±9.32	58.34±6.19	<0.0001
	FEV_1/FVC	72.08±5.90	64.86±6.20	0.0001
30th				
SGRQ	Sputum volume (ml/day)	Nil	39.33±1.0	-
	Dyspnea	3.58±0.02	2.87±0.24	0.0001
	6 MWD test (m)	280.00±10.34	189.76±3.36	<0.0001
	Cough episodes/day	1	5	-
PFT	FVC % predicted	66.12±6.45	62.02±4.43	<0.0001
	FEV_1% predicted	63.05±5.92	59.13±6.24	<0.0001
	FEV_1/FVC predicted	72.12±3.60	64.12±3.80	<0.0001

SGRQ: St. George's Respiratory Questionnaire, PFT: Pulmonary function test, 6 MWD: 6-min walk distance, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity

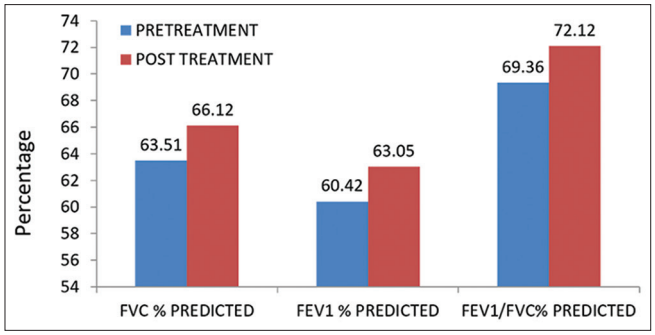

Figure 1: Comparison of pulmonary function tests between pre- and post-treatment among study group after a period of 30 days

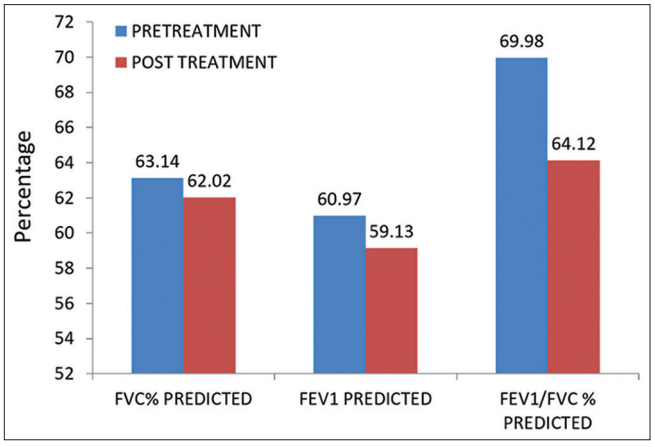

Figure 2: Comparison of pulmonary function tests between pre- and post-treatment among control group after a period of 30 days

the preferred treatment algorithm. The initial treatment was streamlined, i.e., Group A: bronchodilator; Group B: LABA or LAMA; Group C: LAMA; and Group D: LAMA, LABA + LAMA or ICS + LABA. Single-inhaler triple therapy versus ICS plus LABA for COPD (TRILOGY) has been tried effectively.[9]

In this study, the primary effect of low-dose theophylline on CBP (white blood cell [WBC], eosinophil, neutrophils, monocytes, platelet count, and hemoglobin), St. George's respiratory indices, and PFTs (FVC, FEV_1, and FEV_1/FVC) of COPD patients was compared with patients treated without theophylline and the results were analyzed.

No significant improvement in PFTs of the participants was observed. However, blood parameters such as CBP, St. George's respiratory criteria, and daily life were significantly improved in the study group compared to the control group. Theophylline has an anti-inflammatory role in COPD. It inhibits cigarette smoke-induced inflammation in skeletal muscle by upregulating histone deacetylase 2 (HDAC2) expression and decreases NF-KB activation.[10] This can be explained by decreases in dyspnea, air trapping, and breathing

difficulties and increases in diaphragmatic muscle contraction force with theophylline. It decreases the cough episodes as well as improvement in 6MWD. Markham and Faulds[10] reported that theophylline can reduce the eosinophil accumulation in bronchial tissue in the patients with asthma. Hirano *et al*.[11] confirmed that low-dose theophylline reduces the sputum neutrophils. Koo *et al*.[12] in Korea found a significant association between WBC and PFTs among COPD patients, especially noncurrently smoking COPD patients. A decrease in neutrophils was observed in the subjects who were treated with theophylline in this study. This suggests an anti-inflammatory effect of theophylline.

The fall in PFTs in the control group suggests that low-dose theophylline may not improve the PFTs, but it can decelerate the reduction in PFTs. Kirsten *et al*. found worsening of COPD control when theophylline was withdrawn.[13] Similar results were seen by Panahi *et al.*, who assessed the effect of low-dose theophylline on the improvement of PFTs of sulfur mustard-exposed patients.[14]

The cumulative results of this study shown that a low-dose of theophylline can improve the COPD patients' symptoms, but it has minimal effect on the reversal of PFTs into normal. This can be explained by the findings of Gibson *et al.*[15] Theophylline shows its effect by restoring reduced HDAC activity to normal levels, thus suppressing inflammation and potentially making the COPD patients responsive to corticosteroids. Devereux *et al*.[16] demonstrated that low-dose theophylline increases the efficacy of corticosteroids in COPD by reducing the incidence of exacerbations.

In summary, despite an overall lack of benefit, approximately one-third of the patients were subjective responders in both dyspnea and FEV_1 improvement. Selective phosphodiesterase –type 4 inhibito (PDE-4) inhibitors have potential to improve the beneficial effects of theophylline and reduce its adverse effects, although the existing inhibitors appear to be limited by the same side effects as theophylline. In the present study, slight FEV_1 improvement was observed in the study group, but moderate obstruction was persisting with no change in peak expiratory flow rate. Cough episodes were reduced in the study group in 30 days. In the study group, 6 MWD test was improved up to 300 m compared to the control group. Dyspnea subsided in 30 days of treatment with theophylline in compared with control group, and sputum production was reduced significantly. In contrast to our results, other studies[16-18] found no beneficial effect. Further large-scale, long-duration study on a larger population is needed.

Conclusion

Add-on therapy with theophylline improves the clinical condition and spirometric measurements of patients with COPD without an effect on peak expiratory flow rate. Quality of life improvement can be achieved by add-on therapy with theophylline along with ICS, long-acting beta agonists, and LAMA.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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