ORIGINAL ARTICLE

Optimizing Management Beyond Triple Therapy in Stable Severe Chronic Obstructive Pulmonary Disease: Efficacy of Adjunctive Oral Doxophylline in a Randomized Controlled Trial

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition commonly managed with triple inhaler therapy comprising long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS). Despite optimal inhalation therapy, many patients continue to experience persistent symptoms. Doxophylline, a novel xanthine derivative, offers bronchodilator and anti-inflammatory benefits with a more favorable safety profile than traditional methylxanthines.

Objective: To assess the efficacy, safety, and tolerability of oral doxophylline in addition to triple inhaler therapy in patients with stable severe COPD.

Materials and methods: In this randomized controlled trial, 78 patients were allocated to group A (triple therapy + doxophylline 650 mg once daily) and group B (triple therapy alone). Assessment included the COPD assessment test (CAT score), C-reactive protein (CRP), spirometry parameters (FEV_1, FEV_1%, FEV_1/FVC), adverse events, and evaluations were performed on days 0 and 90.

Results: By day 90, group A showed greater improvement in CAT score (7.94 ± 4.17 vs 10.06 ± 3.99; $p = 0.033$) and CRP (12.2 ± 4.47 vs 15.33 ± 5.37 mg/L; $p = 0.01$). Spirometry gains were comparable: FEV_1 (0.97 ± 0.23 vs 0.96 ± 0.26 L/minute; $p = 0.872$), FEV_1% predicted (49.10 ± 8.73 vs 48.69 ± 9.72%; $p = 0.482$), and FEV_1/FVC% (54.09 ± 6.57 vs 52.89 ± 6.95%; $p = 0.397$). Mild adverse events including palpitations (14.29%), tremors (8.57%), and nausea (2.86%) were more frequent in group A but were generally tolerated.

Conclusion: Adjunctive oral doxophylline significantly improved symptom burden and systemic inflammation in patients with stable severe COPD without conferring additional spirometric benefits. Although mild adverse effects were observed, doxophylline was overall well tolerated and may represent a viable adjunctive option in selected COPD patients with persistent symptoms despite optimized inhaler therapy.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a lung condition characterized by persistent inflammation and irreversible airflow limitation, leading to breathing difficulties.[1] It affects 11.7% of the global population and is responsible for approximately 3 million deaths annually, particularly in individuals aged ≥40 years.[2] The pathogenesis of COPD involves both innate and adaptive immune responses, primarily TH1-mediated along with chronic inflammation, protease-antiprotease imbalance, and oxidative stress. These mechanisms contribute to structural damage in the airways and alveoli, influencing symptom severity, disease progression, and treatment responses.[3]

Chronic obstructive pulmonary disease symptoms such as dyspnea, cough, and fatigue are frequently underreported, making tools like COPD assessment test (CAT) and modified Medical Research Council (mMRC) essential for grading severity.[1,4] Diagnosis is confirmed by a postbronchodilator FEV_1/FVC ratio <0.7, although clinical signs may aid in settings without spirometry.[1,5] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 update introduced the ABCD classification to guide therapy based on symptoms and exacerbation risk,[6] while the 2023 revision redefined COPD as a progressive, heterogeneous condition and combined groups C and D into "group E" for frequent exacerbators.[7]

Triple inhaled therapy, including a long-acting β_2 agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS), is recommended for severe COPD, especially in patients with high eosinophil counts or frequent exacerbations. However, some patients remain symptomatic despite this regimen, necessitating additional therapeutic options.[7]

Doxophylline, a xanthine derivative with reduced A1 and A2 receptor affinity, offers bronchodilation with fewer cardiac and neurological adverse effects. Although beneficial in patients with COPD, its role in triple therapy remains underexplored. This study assessed the effectiveness, safety, and tolerability of adding oral doxophylline to triple inhaler therapy in stable severe COPD, per GOLD 2023 guidelines.[8]

Aim

To evaluate the effectiveness, safety, and tolerability of oral doxophylline added to triple drug therapy in patients with stable severe COPD.

Materials and Methods

Trial registration: CTRI/2024/08/071763 (registered on 1st August 2024).

Study Design and Setting

A prospective randomized controlled trial was conducted over 18 months in the Department of Respiratory Medicine, SRM Medical College, with ethics approval and informed consent. Adults aged 40–65 years with COPD (≥6 months) and postbronchodilator FEV_1 <50% were included. Patients with comorbid respiratory or major systemic illnesses, recent MI, or poor inhaler technique were excluded. Patients were followed up for 90 days.

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Sampling and Randomization

Consecutive sampling was performed during outpatient visits. Eligible patients were randomized into two groups using a computer-generated sequence to ensure allocation concealment.

Sample Size Justification

This study was designed as a pilot randomized controlled trial due to limited prior evidence on adjunctive doxophylline in stable severe COPD. A regular sample size calculation was not feasible because of the absence of robust prior effect size data for the primary outcomes (COPD assessment score and C-reactive protein). We aimed for 40 participants per group based on feasibility, recruitment pool over 18 months, and minimum sample size recommendations for pilot RCTs.

Intervention and Methods

Group A received oral doxophylline sustained release 650 mg once daily plus fixed triple inhaler therapy (formoterol 4.8 µg, glycopyrrolate 9 µg, budesonide 160 µg). Group B received triple therapy. Inhalers were administered *via* metered-dose or dry powder devices.

Outcome Measures

Assessments were conducted at baseline, 30, 60, and 90 days. The primary outcomes included changes in the CAT score, serum CRP levels, and spirometric indices (FEV_1 and FEV_1/FVC). Adverse drug reactions and tolerability were also monitored.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) v25.0. Statistical significance was set at $p < 0.05$.

Results

The baseline characteristics were comparable between the groups, with similar mean ages (56.41 ± 4.91 vs 55.28 ± 5.49 years) and male predominance (76.92 vs 79.49%). Cough with expectoration and shortness of breath were reported by 94.87 and 97.44% of the patients, respectively. Smoking history was noted in 74.36% of group A vs 76.92% of group B, with mean pack-years of 29.72 ± 7.86 and 25.73 ± 6.52. Most patients had a normal BMI (64.10 vs 69.23%), while 30.77 vs 28.21% were underweight, and 5.13 vs 2.56% were overweight. Mean hemoglobin was 12.18 ± 1.32 gm/dL (group A) vs 12.34 ± 1.20 gm/dL (group B), with WBC counts of 6717.41 ± 1492.85/mm^3 vs 6344.26 ± 1738.84/mm^3. Chest X-ray findings showed low flat diaphragm (79.49 vs 58.97%), tubular heart (38.46 vs 30.77%), prominent bronchovascular markings (33.33 vs 35.90%), and hyperinflation (46.15 vs 56.41%) (Table 1).

At baseline, GOLD stage distribution was similar between groups, with the severe stage in 31 (79.49%) patients in group A and 32 (82.05%) in group B, and very severe stage in 8 (20.51%) and 7 (17.95%) patients, respectively ($p = 0.774$). The mean CAT score on day 0 was comparable (20.74 ± 3.91 vs 22.23 ± 3.47; $p = 0.08$), but group A showed significantly lower CAT scores at follow-up: day 30 (14.49 ± 3.53 vs 16.49 ± 3.10; $p = 0.013$), day 60 (10.51 ± 4.71

Table 1: Baseline demographic and clinical characteristics

Parameter		*Group A (n = 39)*	*Group B (n = 39)*
Mean age (years) (mean ± SD)		56.41 ± 4.91	55.28 ± 5.49
Gender (male)		30 (76.92%)	31 (79.49%)
Cough with expectoration		37 (94.87%)	37 (94.87%)
Shortness of breath		38 (97.44%)	38 (97.44%)
Smoking history		29 (74.36%)	30 (76.92%)
Mean pack-years		29.72 ± 7.86	25.73 ± 6.52
BMI	Normal	25 (64.10%)	27 (69.23%)
	Underweight	12 (30.77%)	11 (28.21%)
	Overweight	2 (5.13%)	1 (2.56%)
Hematological parameters (mean ± SD)	Hemoglobin (gm/dL)	12.18 ± 1.32	12.34 ± 1.20
	WBC count (/mm^3)	6717.41 ± 1492.85	6344.26 ± 1738.84
Chest X-ray findings, *N* (%)	Low flat diaphragm	31 (79.49%)	23 (58.97%)
	Tubular heart	15 (38.46%)	12 (30.77%)
	Bronchovascular markings	13 (33.33%)	14 (35.90%)
	Hyperinflation	18 (46.15%)	22 (56.41%)

BMI, body mass index; WBC, white blood cell

Table 2: Comparison of GOLD staging: *n* (%), CAT scores, and CRP levels (mean ± SD)

Parameter		*Group A (n = 39)*	*Group B (n = 39)*	*p-value*
GOLD stage	Severe, *n* (%)	31 (79.49%)	32 (82.05%)	0.774
	Very severe, *n* (%)	8 (20.51%)	7 (17.95%)	
CAT score (mean ± SD)	Day 0	20.74 ± 3.91	22.23 ± 3.47	0.08
	Day 30	14.49 ± 3.53	16.49 ± 3.10	0.013
	Day 60	10.51 ± 4.71	12.69 ± 3.97	0.038
	Day 90	7.94 ± 4.17	10.06 ± 3.99	0.033
CRP level (mg/L) (mean ± SD)	Day 0	19.5 ± 6.43	17.11 ± 5.54	0.083
	Day 90	12.2 ± 4.47	15.33 ± 5.37	0.01

$p < 0.05$ significant; CAT, COPD assessment score; CRP-C, reactive protein

Table 3: Comparison of pulmonary function parameters up to 90 days: (mean ± SD)

Parameter	*Time point (days)*	*Group A (mean ± SD)*	*Group B (mean ± SD)*	*p-value*
FEV1 (L/minute)	0	0.77 ± 0.21	0.81 ± 0.23	0.382
	30	0.85 ± 0.20	0.87 ± 0.24	0.732
	60	0.92 ± 0.22	0.93 ± 0.25	0.912
	90	0.97 ± 0.23	0.96 ± 0.26	0.872
FEV1 (% predicted)	0	38.85 ± 8.57	40.74 ± 9.58	0.319
	30	43.64 ± 9.15	44.18 ± 10.01	0.783
	60	46.90 ± 8.67	47.79 ± 9.43	0.673
	90	49.10 ± 8.73	48.69 ± 9.72	0.482
FEV1/FVC (%)	0	46.51 ± 6.68	45.64 ± 7.13	0.544
	30	49.36 ± 6.45	48.38 ± 6.92	0.519
	60	52.36 ± 6.41	51.00 ± 6.79	0.348
	90	54.09 ± 6.57	52.89 ± 6.95	0.397

$p < 0.05$ significant; FEV1, forced expiratory volume in 1st second; FVC, forced vital capacity

Table 4: Comparison of hemodynamic parameters at baseline and day 90: (mean ± SD)

Parameter	*Time point (days)*	*Group A (mean ± SD)*	*Group B (mean ± SD)*	*p-value*
Pulse rate (beats/minute)	0	86.77 ± 5.88	87.51 ± 3.37	0.496
	90	85.23 ± 6.31	86.53 ± 3.25	0.283
Respiratory rate (/minute)	0	18.41 ± 1.57	18.62 ± 1.02	0.495
	90	18.34 ± 1.24	17.89 ± 0.75	0.067
Systolic BP (mm Hg)	0	120.26 ± 7.07	120.77 ± 7.03	0.749
	90	121.43 ± 6.92	118.33 ± 5.61	0.042
Diastolic BP (mm Hg)	0	78.97 ± 7.18	79.49 ± 7.24	0.754
	90	80.00 ± 7.28	75.28 ± 7.74	0.01

BP, blood pressure

vs 12.69 ± 3.97; $p = 0.038$), and day 90 (7.94 ± 4.17 vs 10.06 ± 3.99; $p = 0.033$), indicating better symptom control. Mean CRP levels were similar on day 0 (19.5 ± 6.43 vs 17.11 ± 5.54 mg/L; $p = 0.083$), but significantly lower in group A by day 90 (12.2 ± 4.47 vs 15.33 ± 5.37 mg/L; $p = 0.010$) (Table 2).

The mean FEV_1 (L/minute) was similar between groups A and B throughout the study: day 0 (0.77 ± 0.21 vs 0.81 ± 0.23; $p = 0.382$), day 30 (0.85 ± 0.20 vs 0.87 ± 0.24; $p = 0.732$), day 60 (0.92 ± 0.22 vs 0.93 ± 0.25; $p = 0.912$), and day 90 (0.97 ± 0.23 vs 0.96 ± 0.26; $p = 0.872$). FEV_1 (% predicted) was also comparable on day 0 (38.85 ± 8.57 vs 40.74 ± 9.58; $p = 0.319$), day 30 (43.64 ± 9.15 vs 44.18 ± 10.01; $p = 0.783$), day 60 (46.90 ± 8.67 vs 47.79 ± 9.43; $p = 0.673$), and day 90 (49.10 ± 8.73 vs 48.69 ± 9.72; $p = 0.482$). Similarly, FEV_1/FVC (%) showed no significant difference at baseline (46.51 ± 6.68 vs 45.64 ± 7.13; $p = 0.544$), day 30 (49.36 ± 6.45 vs 48.38 ± 6.92; $p = 0.519$), day 60 (52.36 ± 6.41 vs 51.00 ± 6.79; $p = 0.348$), and day 90 (54.09 ± 6.57 vs 52.89 ± 6.95; $p = 0.397$) (Table 3).

The mean pulse rate was comparable between groups A and B at baseline (86.77 ± 5.88 vs 87.51 ± 3.37; $p = 0.496$) and day 90 (85.23 ± 6.31 vs 86.53 ± 3.25; $p = 0.283$). Respiratory rate also showed no significant difference on day 0 (18.41 ± 1.57 vs 18.62 ± 1.02; $p = 0.495$) or day 90 (18.34 ± 1.24 vs 17.89 ± 0.75; $p = 0.067$). Systolic blood pressure was similar at baseline (120.26 ± 7.07 vs 120.77 ± 7.03; $p = 0.749$), but significantly lower in group B at day 90 (121.43 ± 6.92 vs 118.33 ± 5.61; $p = 0.042$). Diastolic pressure showed no difference at baseline (78.97 ± 7.18 vs 79.49 ± 7.24; $p = 0.754$), yet group B had a significantly lower value at day 90 (80.00 ± 7.28 vs 75.28 ± 7.74; $p = 0.010$) (Table 4).

No adverse effects were reported at the baseline in either group. By day 30, 94.29% of group A and 100% of group B remained free of side effects ($p = 0.233$), with palpitations and tremors observed in 1 patient (2.86%) in group A. At day 60, adverse effects were absent in 85.71% of group A and all of group B ($p = 0.025$); group A reported palpitations (5.71%), tremors (2.86%), and nausea/vomiting (5.71%). By day 90, only 74.29% in group A remained symptom-free compared to 100% in group B ($p = 0.0009$), with 14.29% reporting palpitations, 8.57% tremors, and 2.86% nausea/vomiting (Table 5).

Discussion

This randomized controlled trial evaluated the safety and efficacy of adding oral doxophylline to standard triple therapy in severe COPD, with both groups well matched at baseline to minimize confounding, consistent with findings from a previous study.[9]

Triple therapy combining corticosteroids, LABA, and muscarinic antagonists is standard in COPD management. Formoterol was selected for its potent bronchodilator and anti-inflammatory effects.[10] While major trials (IMPACT, TRIBUTE, ETHOS) confirm the efficacy of triple therapy,[11–13] evidence on the addition of doxophylline, a safer xanthine derivative than theophylline, remains limited.[10]

The doxophylline group experienced earlier and more sustained symptom relief, with significant reductions in CAT scores, indicating better control than triple therapy alone. This aligns with earlier studies showing improved symptom burden and quality of life with doxophylline, supporting its role as a valuable adjunct in COPD treatment.[10,14,15]

Spirometry showed significant improvements in FEV_1, FEV_1%, and FEV_1/FVC in both groups, with no notable intergroup differences, suggesting that lung function improved irrespective of doxophylline. These results are consistent with those of previous studies and major trials such as IMPACT, TRIBUTE, and ETHOS, which reported similar spirometric outcomes.[10–18]

Table 5: Adverse effects over time in both groups: *n* (%)

Time point (days)	*Adverse effect*	*Group A (n = 39)*	*Group B (n = 39)*	*p-value*
0	No adverse effects	39 (100%)	39 (100%)	NA
30	No adverse effects	33 (94.29%)	37 (100%)	0.233
	Palpitations	1 (2.86%)	0 (0%)	
	Tremors	1 (2.86%)	0 (0%)	
60	No adverse effects	30 (85.71%)	36 (100%)	0.025
	Palpitations	2 (5.71%)	0 (0%)	
	Tremors	1 (2.86%)	0 (0%)	
	Nausea and vomiting	2 (5.71%)	0 (0%)	
90	No adverse effects	26 (74.29%)	36 (100%)	0.0009
	Palpitations	5 (14.29%)	0 (0%)	
	Tremors	3 (8.57%)	0 (0%)	
	Nausea and vomiting	1 (2.86%)	0 (0%)	

A previous study in mild-to-moderate COPD (FEV_1 ≥50%) found doxophylline as effective as theophylline-etofylline, with fewer side effects. In contrast, our study in severe COPD (FEV_1 <50%) showed comparable spirometric improvements but greater symptom relief and better CAT scores with doxophylline, suggesting its added benefit in advanced disease.[16]

The FEV_1/FVC ratio improved in both groups during follow-up without significant intergroup differences, consistent with previous studies showing improvements in this parameter with doxophylline therapy.[10,14,15,17,18]

By day 90, the doxophylline group showed a significant reduction in CRP, indicating its anti-inflammatory effect and clinical benefit in COPD. In contrast, the control group showed no significant decrease in CRP levels. These findings align with prior evidence showing greater reduction in inflammatory markers with adjunctive therapies.[15,19]

A previous study also reported a significant CRP reduction with adjunctive therapy, supporting our finding of a greater CRP decline in the doxophylline group. This consistency highlights the potential of doxophylline to reduce systemic inflammation and improve COPD outcomes.[15]

Adverse effects such as palpitations, tremors, and gastrointestinal symptoms were more common in the doxophylline group but were mild and did not require discontinuation, likely due to its partial adenosine receptor activity.[10,14,16,18] Triple therapy alone was well tolerated in this study, although major trials such as IMPACT, TRIBUTE, and ETHOS have reported systemic and respiratory-related side effects even with triple therapy.[11–13]

Clinical Implications

In clinical practice, adjunctive doxophylline may be considered for patients with stable severe COPD who remain symptomatic despite optimal triple inhaler therapy, and in those with systemic inflammation (e.g., raised CRP) and no contraindications to xanthine derivatives. Its favorable safety profile compared to theophylline, along with once-daily dosing in its sustained release preparation, may aid adherence in selected patients. However, mild cardiovascular or gastrointestinal side effects should be monitored. Additionally, doxophylline may have a steroid-sparing role in individuals who are unable to tolerate high-dose inhaled corticosteroids, enabling maintenance of symptom control without escalation beyond medium ICS doses.

Conclusion

Adding doxophylline to triple therapy in stable severe COPD improved symptom control and reduced CRP levels, with similar spirometric gains to triple therapy alone. Although mild adverse effects such as palpitations and tremors were more frequent, doxophylline was well tolerated and did not affect exacerbation rates. It shows promise as an adjunct in severe COPD; however, long-term studies are needed to confirm its safety and efficacy.

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