Original Article

Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients with COPD: A Randomized Clinical Trial

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease characterized by chronic inflammation and irreversible airflow obstruction, leading to frequent exacerbations that significantly impair quality of life. Standard treatments, including inhaled corticosteroids (ICS), show variable efficacy in preventing exacerbations, highlighting the need for adjunct therapies.

Objective: This study aims to investigate the efficacy and safety of adding low-dose theophylline to ICS therapy in reducing the frequency and severity of exacerbations in COPD patients.

Methods: A randomized, double-blind, placebo-controlled clinical trial was conducted from March 2024 to October 2024, involving 200 adults diagnosed with COPD. Participants were assigned to receive either ICS plus low-dose theophylline (200 mg twice daily) or ICS alone. The primary outcome was the frequency of exacerbations requiring antibiotics or corticosteroids over 6 months, with secondary outcomes including lung function, quality of life, and adverse events.

Results: The addition of low-dose theophylline significantly reduced the mean number of exacerbations (2.27 vs. 2.76, $P < 0.0001$) and hospital admissions (0.15 vs. 0.27, $P < 0.0001$) compared to ICS alone. Improvements in FEV1 % predicted and COPD Assessment Test (CAT) scores were also observed, with significant differences noted at 6 months. Safety analysis indicated a higher incidence of non-serious and serious adverse drug reactions in the combination group, but pneumonia cases and mortality rates were comparable between groups.

Conclusion: The study concludes that low-dose theophylline as an adjunct to ICS therapy provides significant clinical benefits in managing COPD, including reduced exacerbations, improved lung function, and enhanced quality of life, with an acceptable safety profile. Further research is warranted to validate these findings and explore optimal dosing strategies.

Keywords: COPD, Inhaled Corticosteroids, Theophylline, Exacerbations, Lung Function, Quality of Life.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease that significantly impairs the quality of life for millions of people globally.[1, 2] It is characterized by chronic inflammation and irreversible airflow obstruction, leading to frequent exacerbations. These exacerbations, often triggered by infections or environmental factors, can cause severe respiratory distress, hospitalization, and even increased mortality.[3] Hence, preventing and managing exacerbations is a critical aspect of COPD treatment. Standard treatments include inhaled corticosteroids (ICS) to reduce inflammation and improve lung function, but their efficacy in preventing exacerbations varies among patients.[4] This variability underscores the need for adjunct therapies to enhance treatment outcomes.

Theophylline, a bronchodilator and anti-inflammatory agent, has been used for decades in the management of respiratory diseases like asthma and COPD. Despite its established benefits, theophylline's narrow therapeutic window and potential side effects have led to its reduced use in favour of newer medications.[5] However, recent studies have suggested that low-dose theophylline may still offer significant benefits when used as an adjunct to ICS, potentially reducing the frequency and severity of exacerbations in COPD patients.[1, 6-8] This study aims to investigate the efficacy and safety of adding low-dose theophylline to ICS therapy in reducing COPD exacerbations.

The rationale for combining theophylline with ICS is based on their complementary mechanisms of action. While ICS primarily target inflammation, theophylline exerts bronchodilatory effects and enhances mucociliary clearance, potentially providing a dual therapeutic approach to managing COPD. Additionally, low-dose theophylline has been shown to inhibit phosphodiesterase enzymes and enhance the anti-inflammatory effects of corticosteroids. These properties suggest that theophylline could amplify the benefits of ICS, leading to better control of COPD symptoms and exacerbations.[1, 6-8]

The findings of this study have the potential to influence clinical practice by providing evidence on the benefits and

risks of adding theophylline to ICS therapy in COPD management. If successful, this combination therapy could offer a new approach to reducing exacerbations and improving the overall health of COPD patients. It could also provide insights into the optimal use of older medications like theophylline in contemporary treatment regimens.

This study seeks to explore the research question: "Does the addition of low-dose theophylline to inhaled corticosteroid (ICS) therapy reduce the frequency and severity of exacerbations in patients with COPD?" The hypothesis is that low-dose theophylline, when used as an adjunct to ICS, will significantly decrease the incidence of COPD exacerbations compared to ICS therapy alone. The primary objective of this randomized clinical trial is to evaluate the efficacy and safety of theophylline as an adjunct to ICS in reducing COPD exacerbations, with secondary objectives including the assessment of lung function, quality of life, and adverse events associated with this combined therapy.

This study seeks to address a significant gap in COPD treatment by evaluating the role of theophylline as an adjunct to ICS. By employing a robust clinical trial design and focusing on relevant clinical outcomes, the research aims to provide valuable data that could enhance our understanding of COPD management and potentially improve patient outcomes.

MATERIALS & METHODS

Trial Design

This study was a randomized, double-blind, placebo-controlled clinical trial designed to evaluate the efficacy and safety of low-dose theophylline as an adjunct to inhaled corticosteroid (ICS) therapy in reducing exacerbations in patients with COPD. The study was conducted in Department of Pharmacology of NMCH, Patna in collaboration with Department of General Medicine from March 2024 to October 2024.

Participants

Participants were adults diagnosed with COPD, aged 40-75 years, with a history of at least one exacerbation in the past year. Exclusion criteria included severe comorbidities, contraindications to theophylline, and current use of other bronchodilators.

Interventions

Participants were randomly assigned to receive either ICS plus low-dose theophylline (ICS +T) or ICS alone. Theophylline was administered at a dose of 200 mg twice daily. Both groups continued their regular ICS therapy.

Outcomes

The primary outcome was the frequency of COPD exacerbations “requiring antibiotics, oral corticosteroids, or both” over a 6-month period.

Secondary Outcome Measures:

- “Participant-reported unscheduled hospital admissions because of severe exacerbations of COPD[9]
- COPD-related health status (COPD Assessment Test [CAT] scale, 0 to 40 with ≤5 being the norm for healthy nonsmokers and >30 indicating a very high COPD effect on quality of life[10]
- Modified Medical Research Council (mMRC) dyspnea score (range, 0 [not troubled by breathlessness except on strenuous exercise] to 4 [too breathless to leave the house or breathless when dressing or undressing])[11]
- Post bronchodilator spirometry (FEV_1/FVC as percent predicted)[12, 13]
- Adverse reactions or serious adverse events”

Sample Size

Sample size was calculated based on previous studies, aiming for 80% power to detect a 20% reduction in exacerbation frequency with a significance level of 0.05. A total of 200 participants were enrolled, with 100 in each group.

Randomization

Participants were randomly assigned in a 1:1 ratio using a computer-generated randomization sequence. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes.

Recruitment and Baseline Data

Participants were recruited from outpatient clinics and community advertisements. Baseline demographic and clinical characteristics were collected and compared between groups to ensure balance.

Follow-up

Participants were followed up monthly to assess exacerbation rates, lung function, and quality of life. Adverse events were recorded and managed according to predefined criteria.

Statistical Analysis

In this study, descriptive statistics were used to summarize baseline demographic and clinical characteristics, including age (mean ± SD), gender distribution, smoking status, and use of long-term antibiotics in both the ICS + T and ICS groups. Fisher's Exact Test compared categorical variables with small sample sizes, such as gender distribution and current smoker status, to identify significant differences between the groups. The unpaired t-test compared means of continuous variables, such as age, exacerbations in the last 6 months, COPD hospital admissions, FEV1 % predicted, and CAT scores between the groups. The Chi-Square Test analyzed the distribution of categorical variables, such as mMRC dyspnea scores and

safety parameters (pneumonia, mortality, adverse drug reactions) between the groups. P-values assessed the significance of differences observed, with a P-value less than 0.05 considered statistically significant.

RESULTS

Table 1: Comparison of baseline demographic and clinical characteristics between ICS plus low-dose theophylline (ICS +T) vs ICS Group

Parameters	ICS + T (n=100)	ICS (n=100)	P-value
Age in Years, mean ± SD	64.47 ± 7.36	65.13 ± 9.21	0.576237*
Male / Female, n	56/44	58/42	0.8865**
Current Smoker, n	32	35	0.7646**
Long-term antibiotics, n	8	10	0.8056**
Exacerbations in last 6 months, mean ± SD	3.74 ± 0.52	3.62 ± 0.75	0.190072*

** Fisher's Exact Test **Unpaired t-test*

The average age in both groups was similar (64.47 ± 7.36 years in ICS + T and 65.13 ± 9.21 years in ICS), with no significant difference (P = 0.576). The gender distribution was almost equal in both groups (56 males/44 females in ICS + T and 58 males/42 females in ICS), with a non-significant P-value of 0.8865. The proportion of current smokers was also comparable (32 in ICS + T and 35 in ICS, P = 0.7646). The number of participants on long-term antibiotics was slightly higher in the ICS group (10) compared to the ICS + T group (8), with a non-significant P-value of 0.8056. Overall, the baseline characteristics of the two groups were well-matched, showing no significant differences. [Table 1]

Table 2: Comparison of exacerbation and COPD hospital admission between ICS plus low-dose theophylline (ICS +T) vs ICS Group

Parameters	Value in mean ± SD		P-value (Unpaired t-test)
	ICS + T (n=100)	ICS (n=100)	
Exacerbation	2.27 ± 0.32	2.76 ± 0.43	<0.0001
COPD hospital admission	0.15 ± 0.04	0.27 ± 0.06	<0.0001

The mean number of exacerbations was significantly lower in the ICS + T group (2.27 ± 0.32) compared to the ICS group (2.76 ± 0.43), with a P-value of <0.0001. Similarly, the mean number of COPD hospital admissions was significantly lower in the ICS + T group (0.15 ± 0.04) compared to the ICS group (0.27 ± 0.06), with a P-value of <0.0001. These results indicate that the addition of low-dose theophylline to ICS therapy significantly reduced both exacerbations and hospital admissions due to COPD. [Table 2]

Table 3: Comparison of FEV_1 % predicted between ICS plus low-dose theophylline (ICS +T) vs ICS Group

Time	Value in mean ± SD		P-value (Unpaired t-test)
	ICS + T (n=100)	ICS (n=100)	
Baseline	52.42 ± 7.23	52.53 ± 7.65	0.916875
1 Month	53.59 ± 7.25	52.84 ± 7.68	0.478461
3 Months	54.67 ± 7.27	53.08 ± 7.70	0.134832
6 Months	56.78 ± 6.30	53.79 ± 6.72	**0.001374**

At baseline, the FEV1 % predicted was similar between the groups (52.42 ± 7.23 in ICS + T and 52.53 ± 7.65 in ICS), with no significant difference (P = 0.916875). After 6 months, the FEV1 % predicted improved significantly in the ICS + T group (56.78 ± 6.30) compared to the ICS group (53.79 ± 6.72), with a P-value of 0.001374. These results indicate that the addition of low-dose theophylline to ICS therapy significantly improved FEV1 % predicted over time, especially after 6 months. [Table 3]

Table 4: Comparison of CAT Score between ICS plus low-dose theophylline (ICS +T) vs ICS Group

Time	Value in mean ± SD		P-value (Unpaired t-test)
	ICS + T (n=100)	ICS (n=100)	
Baseline	22.83 ± 4.56	22.94 ± 4.78	0.867926
1 Month	21.47 ± 4.50	22.39 ± 4.75	0.161275
3 Months	20.75 ± 4.45	22.01 ± 4.69	0.052720
6 Months	19.09 ± 4.37	21.42 ± 4.62	**0.000319**

At baseline, the CAT Scores were similar between the groups (22.83 ± 4.56 in ICS + T and 22.94 ± 4.78 in ICS), with no significant difference (P = 0.867926). After 6 months, the CAT Scores improved significantly in the ICS + T group (19.09 ± 4.37) compared to the ICS group (21.42 ± 4.62), with a P-value of 0.000319. These results indicate that the addition of low-dose theophylline to ICS therapy significantly improved the CAT Scores over time, especially after 6 months. [Table 4]

Table 5: Comparison of mMRC dyspnea score at 6 Months between ICS plus low-dose theophylline (ICS +T) vs ICS Group

mMRC dyspnea score	Number of Patients		P-value (Chi-Square Test)
	ICS + T (n=100)	ICS (n=100)	
0: Breathless strenuous exercise	7	5	0.7452
1: Breathless hurrying	29	25	
2: Slower than contemporaries	28	26	
3: Stop after 100 m	27	30	
4: Breathless leaving house	9	14	

Those who had to stop after 100 meters (score 3) included 27 patients in the ICS + T group and 30 in the ICS group. Finally, the number of patients who were breathless upon leaving the house (score 4) was 9 in the ICS + T group and 14 in the ICS group. These results indicate that the distribution of dyspnoea scores at 6 months was relatively similar between the two groups. [Table 5]

Table 6: Comparison of Safety between ICS plus low-dose theophylline (ICS +T) vs ICS Group

Parameters	Number of Patients	
	ICS + T (n=100)	ICS (n=100)
Pneumonia	7	5
Mortality	1	2
Adverse Drug Reaction (Non-Serious)	51	42
Adverse Drug Reaction (Serious)	11	9

The number of pneumonia cases was 7 in the ICS + T group and 5 in the ICS group. Mortality was slightly higher in the ICS group, with 2 deaths compared to 1 in the ICS + T group. There were more non-serious adverse drug reactions in the ICS + T group (51) compared to the ICS group (42). Similarly, serious adverse drug reactions were slightly higher in the ICS + T group (11) compared to the ICS group (9). These results suggest that while the addition of low-dose theophylline to ICS therapy may increase the number of adverse drug reactions, both serious and non-serious, the differences in pneumonia cases and mortality between the two groups were minimal. [Table 6]

DISCUSSION

Our study's findings, demonstrating significant clinical benefits of adding low-dose theophylline to ICS therapy, align with certain aspects of previous research while diverging on others.

The scientific background of our study's findings revolves around the pharmacological effects of theophylline and its role in managing chronic obstructive pulmonary disease (COPD). Theophylline is a bronchodilator that works by inhibiting phosphodiesterase, leading to an increase in intracellular cyclic AMP and subsequent relaxation of bronchial smooth muscle. This mechanism helps in reducing airway obstruction, thus improving airflow in patients with COPD. Additionally, theophylline has anti-inflammatory properties that can modulate the immune response, reducing inflammation in the airways. When combined with inhaled corticosteroids (ICS), which primarily reduce inflammation and improve lung function, theophylline can enhance the overall therapeutic effect by targeting multiple pathways involved in COPD pathology.

Our study demonstrated that the addition of low-dose theophylline to ICS therapy resulted in significant clinical benefits, including a reduction in exacerbations and hospital admissions, as well as improvements in lung function as evidenced by the FEV1 % predicted. These outcomes suggest that the combination therapy not only addresses the symptoms of COPD but also modulates the underlying inflammatory processes more effectively than ICS alone. The observed improvement in patient-reported outcomes, such as the CAT score, further supports the synergistic effect of this combination, highlighting its potential to provide better management and quality of life for COPD patients. These findings are particularly relevant in the context of optimizing COPD treatment regimens to achieve better control over the disease and reduce healthcare burden.

Preclinical investigations have shown that the incorporation of low-dose theophylline with ICS therapy produces a cumulative anti-inflammatory effect.[14] The previous RCTs of low-dose theophylline were relatively small (58-110 individuals), yielded inconsistent outcomes, and exhibited significant limitations. [15-17]

Suai T et al. (2021) found that theophylline as an add-on to ICS did not reduce COPD exacerbations and was associated with higher hospitalization and mortality rates.[6] In contrast, our study showed a significant reduction in exacerbations and COPD hospital admissions with theophylline addition. This discrepancy might be due to differences in sample size, population characteristics, or the specific dosing regimens used. **Wilairat P et al. (2019)** reported an increased risk of overall exacerbation with theophylline but not a significant increase in hospitalizations for exacerbation or pneumonia.[7] Our study similarly observed a manageable safety profile but with a reduction in exacerbations and hospital admissions,

suggesting that theophylline's effect might vary based on treatment contexts or patient adherence.

Ford PA et al. (2010) demonstrated improvements in lung function and inflammatory markers with ICS and theophylline combination.[8] This aligns with our finding of significant improvement in FEV1 % predicted, reinforcing the potential benefits of combination therapy in enhancing lung function. **Devereux G et al. (2018)** did not find a significant difference in exacerbation rates between theophylline and placebo groups.[1] However, our study indicated a clear benefit in reducing exacerbations with theophylline addition. This could be attributed to variations in study design, patient populations, or follow-up durations.

Overall, our study supports the clinical utility of low-dose theophylline as an adjunct to ICS therapy in managing COPD, with observed benefits in reducing exacerbations and hospital admissions, along with improvements in lung function, contrasting with some prior findings while corroborating others. Further large-scale studies are warranted to consolidate these findings and address the discrepancies observed.

Despite the promising findings, our study has several limitations. Firstly, the sample size, though adequate, might not fully represent the diverse population of COPD patients, potentially limiting the generalizability of the results. Secondly, the study's duration, while sufficient to observe significant changes, may not capture long-term effects and safety of the combination therapy. Thirdly, the reliance on self-reported measures for certain outcomes, such as exacerbations, can introduce reporting bias. Additionally, adherence to medication, which plays a crucial role in treatment efficacy, was not rigorously monitored, potentially affecting the results. Lastly, the study did not explore the impact of varying doses of theophylline, which could provide more nuanced insights into its optimal use alongside ICS therapy. Future research should address these limitations to strengthen the evidence base for the combined use of low-dose theophylline and ICS in COPD management.

CONCLUSION

This study concludes that the addition of low-dose theophylline to ICS therapy in patients provided significant clinical benefits. Specifically, it significantly reduced exacerbations and hospital admissions due to COPD, a significant improvement in FEV1 % predicted over 6 months and a notable reduction in CAT scores, indicating an improvement in patient-reported outcomes over the same period. In terms of safety, while there was a higher number of non-serious and serious adverse drug reactions in the ICS + T group, the differences in pneumonia cases and mortality between the groups were minimal. Overall, the combination therapy of ICS plus low-dose theophylline demonstrated superior efficacy in managing COPD symptoms and improving lung function with a manageable safety profile.

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REFERENCES

1. Devereux G, Cotton S, Fielding S, et al. Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD: A Randomized Clinical Trial. JAMA. 2018 Oct 16;320(15):1548-1559. doi: 10.1001/jama.2018.14432. PMID: 30326124; PMCID: PMC6233797.
2. Adeloye D, Chua S, Lee C, et al. . Global and regional estimates of COPD prevalence. J Glob Health. 2015;5(2):020415. doi: 10.7189/jogh.05.020415
3. Agarwal AK, Raja A, Brown BD. Chronic Obstructive Pulmonary Disease. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559281/
4. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020 May 1;201(9):e56-e69. doi: 10.1164/rccm.202003-0625ST. Erratum in: Am J Respir Crit Care Med. 2020 Sep 15;202(6):910. doi: 10.1164/rccm.v202erratum5. PMID: 32283960; PMCID: PMC7193862.
5. Jilani TN, Preuss CV, Sharma S. Theophylline. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519024/
6. Shuai T, Zhang C, Zhang M, Wang Y, Xiong H, Huang Q, Liu J. Low-dose theophylline in addition to ICS therapy in COPD patients: A systematic review and meta-analysis. PLoS One. 2021 May 24;16(5):e0251348. doi: 10.1371/journal.pone.0251348. PMID: 34029327; PMCID: PMC8143407.
7. Wilairat P, Kengkla K, Thayawiwat C, Phlaisaithong P, Somboonmee S, Saokaew S. Clinical outcomes of theophylline use as add-on therapy in patients with chronic obstructive pulmonary disease: A propensity score matching analysis. Chron Respir Dis. 2019 Jan-Dec;16:1479973118815694. doi: 10.1177/1479973118815694. PMID: 30558448; PMCID: PMC6302972.
8. Ford PA, Durham AL, Russell RE, Gordon F, Adcock IM, Barnes PJ. Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD. Chest. 2010 Jun;137(6):1338-44. doi: 10.1378/chest.09-2363. Epub 2010 Mar 18. PMID: 20299628.
9. Celli BR, MacNee W; ATS/ERS Task Force . Standards for the diagnosis and treatment of patients with COPD. Eur Respir J. 2004;23(6):932-946. doi: 10.1183/09031936.04.00014304

10. CAT Governance Board COPD assessment test 2016. http://www.catestonline.org/. Accessed July 2, 2024.

11. Fletcher CM. Standardised questionnaire on respiratory symptoms. BMJ. 1960;2:1665. doi: 10.1136/bmj.2.5213.166513688719

12. Miller MR, Hankinson J, Brusasco V, et al. ; ATS/ERS Task Force . Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338. doi: 10.1183/09031936.05.00034805

13. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014;189(3):250-255. doi: 10.1164/rccm.201310-1863PP

14. Barnes PJ. Theophylline. Am J Respir Crit Care Med. 2013;188(8):901-906. doi: 10.1164/rccm.201302-0388PP

15. Zhou Y, Wang X, Zeng X, et al. . Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. Respirology. 2006;11(5):603-610. doi: 10.1111/j.1440-1843.2006.00897.x

16. Cosío BG, Shafiek H, Iglesias A, et al. . Oral low-dose theophylline on top of inhaled fluticasone-salmeterol does not reduce exacerbations in patients with severe COPD. Chest. 2016;150(1):123-130. doi: 10.1016/j.chest.2016.04.011

17. Subramanian R, Ragulan, Jindal A, Viswambhar V, Arun Babu V. The study of efficacy, tolerability and safety of theophylline given along with formoterol plus budesonide in COPD. J Clin Diagn Res. 2015;9(2):OC10-OC13.