Original Article

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The Study of Efficacy, Tolerability and Safety of Theophylline Given Along with Formoterol Plus Budesonide in COPD

Internal Medicine Section

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a common disease causing significant socioeconomic burden. COPD patients, commonly smokers develop resistance to inhaled steroids attributed to deficiency of histone deacetylase 2 (HDAC2). The study of relationship between systemic inflammation and functional performance demonstrated that increased CRP level is inversely related to six minute walk distance (SMWD) and Forced Expired Volume in one second (FEV1). Theophylline restores HDAC2 activity thereby unlocking steroid resistance and potentiating inhaled corticosteroids (ICS) action culminating in reduced airway inflammation and mortality.

Aim: To study the effects of addition of Theophylline to the combination of Formoterol plus Budesonide on various objective and subjective parameters in moderate to severe COPD patients and to assess the safety profile of the combination.

Setting and Study design: A single blinded, prospective, randomized, placebo controlled study at a tertiary care hospital in Jaipur, India.

Materials and Methods: Fifty eight patients diagnosed with moderate to severe COPD were randomized into two groups. Group A patients received Formoterol 24µg plus budesonide 800µg daily in divided doses along with Theophylline while group B patients received Formoterol 24µg plus budesonide 800µg daily in divided doses along with placebo tablets. Both groups were followed up on 15th, 30th & 60th day. During every visit all patients were assessed subjectively (symptom scoring) and objectively (spirometry, CRP, SMWT) and adverse effects if any were recorded. The obtained data subject to statistical analysis using"Graph pad Instat3" software.

Results: Statistically significant improvement with a decline in total symptom score ($p < 0.0001$) was found with respect to "Night symptoms"& "SOB on rising" in group A. Theophylline group showed significant improvement in SMWD and FEV1. Mean fall in CRP was greater in Group A (not statistically significant). No side effects requiring withdrawal of drug were noted with Theophylline.

Conclusion: Addition of Theophylline to Formoterol plus Budesonide reduces dyspnea, improves exercise performance and pulmonary functions in moderate to severe COPD. Further studies are required to explore if reduced dosage would have equal efficacy with better safety and tolerability profile.

Keywords: COPD, CRP, Histone deacetylase, Theophylline

INTRODUCTION

COPD is a serious and disabling disease, which imposes a large burden on the patients, the healthcare system and the society. In COPD, lung function deteriorates progressively over several years with increasing symptoms. Acute exacerbations are common particularly in later stages [1], and these have considerable impact on patient's daily activities and well-being [2]. Cigarette smoking is the major etiological factor in COPD.

The pharmacotherapy of COPD has largely consisted of bronchodilators such as β2-agonists, anticholinergics [3] and theophylline. Studies have not consistently shown theophylline to be beneficial in the management of stable COPD [4-6]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [7] recommends use of theophylline as a second line option after treatment with β2-agonists and anticholinergics. COPD patients develop resistance to the anti-inflammatory effects of ICS attributed to the deficiency of HDAC2 [8]. Theophylline has the property of restoring HDAC2 activity and thereby unlock steroid resistance. Thus it may reduce airway inflammation in COPD [9,10].

The relationship between systemic inflammation and functional performance has been studied [11,12] in COPD patients and it was found that increased CRP levels is indirectly related to SMWD and FEV1. Inhaled steroids can reduce systemic CRP in COPD and that this may be linked with decreased mortality [13-15]. Theophylline by restoring the HDAC2 levels in COPD may potentiate this action of ICS.

The role of theophylline to the combination of formoterol and budesonide on various parameters like FEV1, six-minute walk test, C-reactive protein and quality of life in stable moderate to severe COPD patients is not clearly defined, more particularly in Indian patients.

MATERIALS AND METHODS

The study was conducted at Department of Pulmonary Medicine, S.M.S. Medical College and Hospital, Jaipur for a period of one year. Patients with moderate-to-severe COPD according to GOLD guidelines [7] were included. The diagnosis of COPD was based on clinical history, physical examination, smoking status (pack per year), radiological picture and spirometry.

Inclusion criteria

1. COPD symptoms for ≥two yrs.
2. FEV1/FVC ≤ 70%, FEV1 ≤80% predicted (stages II & III - GOLD)[7].

Exclusion criteria

1. Exacerbation within three months,
2. History of asthma or FEV1 increased more than 12% or 200 ml after bronchodilation,
3. Current respiratory tract disorders other than COPD (like bronchial carcinoma, tuberculosis, pneumonia),
4. Other significant extra pulmonary diseases that can influence the results of the study.

All the patients included in the study were investigated with detailed clinical history including family history, thorough physical examination, sputum smear examination by Ziehl-Neelson method, blood investigations including Haemoglobin, Total Leucocyte Count, Differential Count, Total eosinophil count, fasting blood sugar, liver function tests and renal function tests, HIV serology, C-Reactive protein, complete urine examination, electrocardiography and spirometry. The scoring system for each symptom allowed values in the range from 0 (no symptoms) to three (worst), and the six questions (ability to perform the usual daily activities, breathlessness over the previous 24 hours, waking at night due to respiratory symptoms, breathlessness on rising, cough, sputum production) allowed for up to a maximum total score of 18.

Randomization: Fifty-eight patients satisfying above mentioned inclusion criteria were included in the study. Informed written consent was obtained from all patients. Following medications were withdrawn from all subjects prior to start of the study - systemic steroid treatment for four weeks; inhaled steroids for two weeks; inhaled long-acting β2-agonists for 48 hours. The subjects were randomized into two groups A & B. Group A patients received Formoterol 24µg plus budesonide 800µg daily in divided doses by metered dose inhaler (MDI) and Theophylline according to weight (patients > 50 kg received 400 mg, 40-50 kg received 300 mg and < 40 kg received 200 mg once daily). Group B patients received Formoterol 24µg plus budesonide 800µg daily in divided doses with MDI and similarly looking placebo tablets.

Follow up: All patients were followed up on 15th, 30th & 60th day and assessed subjectively (symptom scoring) and objectively (spirometry, serum CRP, Six minute walk Test) and adverse effects if any was recorded. The obtained data was analyzed with Students t test, Chi square test, non parametric tests for unpaired data and correlation tests using "Graph pad Instat3 statistical software".

RESULTS

Baseline Clinical profile: Of the 58 patients enrolled 50 completed the study, six patients were lost to follow up and two patients developed exacerbation within seven days. As shown in [Table/Fig-1], both group A & B had comparable baseline characteristics.Breathlessness, cough & expectoration were the predominant symptoms and mean duration of illness in group A was 7.5 ± 8.12 years in group B and 6.42 ± 5.74 years (p = 0.77) and majority were current smokers.

CRP levels and its correlation with various parameters in both groups: The mean value of serum CRP in group A and group B at baseline was similar (6.25 ± 1.52 mg/dl and 5.53 ± 1.9 mg/dl). Base line CRP levels were found to be directly correlated with symptom score and inverse correlation with FEV1 and SMWD. Age and pack years did not have any correlation with CRP levels.The mean change of CRP levels at the end of two months in group A & B was -1.25 ± 0.76 & -1.04 ± 0.73 mg/dl respectively. (p - 0.26) as shown in [Table/Fig-2].

Symptom score, FEV1 and SMWD change in both groups: Significant improvement was found with respect to "Night symptoms"& "SOB on rising" in group A. Decline in Total symptom score at the end of two months was more in group A (p < 0.0001)as shown in [Table/Fig-3]. The mean change in FEV1 at the end of two months was more in group A than group B (260 ± 50 ml & 210 ± 80 ml respectively, p - 0.01) as shown in [Table/Fig-4]. Mean change of SMWD at the end of two months in group A & group B was 27.75 ± 7.66 meters & 19.81 ± 6.30 meters respectively (p < 0.05) as shown in [Table/Fig-5] .

Side Effect Profile: At the end of two months of therapy side effects in the form of nausea, vomiting, head ache, palpitation and insomnia were more in group A than group B but none of these required withdrawal of the drug.

Parameter	Group A	Group B	p- value
Age	57.96 ± 7.47	54.46 ± 10.49	0.18
Sex	M 21: 3F	25M: 1F	0.54
Symptoms	Dyspnea (100%)	Dyspnea (100%)	1
	Cough &exp (92)	Cough &exp (88%)	0.70
	Chest pain (42%)	Chest pain (42%)	0.96
Duration	7.5 ± 8.12	6.42 ± 5.74	0.77
Smoking habit	12 Smokers	15 Smokers	0.83
	8 Ex Smokers	5 Ex Smokers	
	4 Reformed Smokers	6 Reformed Smokers	
Pack years	42.17 ± 17.46	37.12 ± 16.12	0.32
Past ATT (+)	2	5	0.48
BMI	16.38 ± 2.81	17.50 ±2.52	0.14
Haemoglobin	10.84 ± 1.56	11.32 ± 1.48	0.27
Pulse	82.75 ± 5.77	83 ± 5.69	0.87
Systolic BP	122.58 ± 8.12	124.50 ± 9.18	0.43
Diastolic BP	78.83 ± 4.45	78.46 ± 4.64	0.77
RR	20.67 ± 2.33	18.7 ± 2.19	0.003
GOLD stage	11mod.: 13 severe	19 moderate: 7severe	0.09
CRP –D0	6.25± 1.52	5.53 ± 1.9	0.09
SMWD – D0	373.17 ± 79.21	408.62 ± 55.82	0.07
FEV1% predicted	49.33 ± 14.79	56.92 ± 12.78	0.05
FEV1/FVC %	54.08 ± 11.81	58.81± 7.98	0.10

[Table/Fig-1]: Baseline characteristics amongst the two groups

Group	Mean ± S.D. of Serum Crp				Mean Change D0 – D60
	D0	D15	D30	D60	
A	6.25± 1.52	5.83 ±1.50	5.49 ± 1.47	5 ± 1.33	1.25 ± 0.76
B	5.53 ± 1.9	5.16±1.83	4.86 ± 1.76	4.49 ±1.61	1.04 ± 0.73
p - value	t - 1.68	t - 1.41	t - 1.37	t - 1.22	p - 0.26 *
	p - 0.09	p - 0.17	p - 0.18	p - 0.23	

[Table/Fig-2]: Mean ± S.D. of Crp levels in both groups

Group	Mean (± S.D) of TSS				Mean Change D0 – D60
	D0	D15	D30	D60	
A	10.17 ± 2.30	9.58 ± 2.26	7 ± 2.48	5.33 ± 1.99	4.88 ± 0.9
B	8.35 ± 1.87	7.92 ±1.92	6.04 ±2.14	4.88 ± 2.03	3.46 ± 1.03
p - value	t -3.08	t - 2.80	t - 1.47	t - 0.79	t = 5.17 p = 0.0001
	p -0.003	p -0.007	p - 0.14	p - 0.43	

[Table/Fig-3]: Mean (± S.D) of total symptom score in both groups

Group	Mean (±S.D) of Absolute Fev1				Mean Change D0 – D60
	D0	D15	D30	D60	
A	1.16 ±0.45	1.24 ±0.47	1.32 ± 0.48	1.42 ± 0.46	0.26 ± 0.05
B	1.42 ±0.46	1.49±0.47	1.56 ± 0.48	1.64 ± 0.51	0.21 ± 0.08
p - value	t = 2.02	t = 1.87	t = 1.76	t = 1.59	t = 2.62 p = 0.01
	p = 0.04	p = 0.06	p = 0.08	p = 0.11	

[Table/Fig-4]: Mean (± S.D) of absolute fev1 in both groups

Group	Mean ± S.D of SMWD				Mean Change D0 – D60
	D0	D15	D30	D60	
A	373.17±79.21	382.04±80.05	391.42±81.22	400.92± 80.32	27.75 ±7.66
B	408.62±55.82	418.38±57.94	423.73±57.94	428.38± 58.79	19.81 ±6.30
p-value	t = 1.84	t = 1.85	t = 1.62	t = 1.38	t = 4.01 p=0.0002
	p = 0.07	p = 0.07	p = 0.11	p = 0.17	

[Table/Fig-5]: Mean (± S.D) of absolute fev1 in both groups

DISCUSSION

Serum CRP levels in COPD: In the present study only stable patients with moderate to severe COPD were included and inspite of this, serum CRP levels were raised (> 5 mg/L) in 60% (n = 30) patients. The relation of elevated CRP levels with COPD has been reported in various population-based studies [16,17] which is in line with definition of COPD as a systemic disease. Of these 30 patients who had elevated CRP levels, 20 patients belonged to stage III COPD and 10 patients belonged to stage II disease. The mean CRP level in our study was 5.9mg/L.

CRP levels and its correlation with various parameters in both groups: CRP levels were inversely correlated to FEV1, BMI and SMWD and directly correlated to the symptom score. Age and intensity of smoking did not have any correlation with CRP levels. Previous reports on this aspect are not consistent, while Dentener MA et al., [18] and Pinto-Plata et al., [12] did not find a correlation between CRP levels and lung function. NHANES - III [16] showed an inverse relation between systemic CRP and FEV1 even in non-COPD patients. This was also found in the Caerphilly Prospective Heart Disease Study [19], which included only male patients with ischemic heart disease. The inverse correlation of CRP with SMWD was reported by Broekhuizen et al., [20]. Pinto-Plata et al., [12] also reported decreased SMWD as the most important clinically relevant predictor of elevated CRP levels.

Effect of inhaled steroids on serum CRP levels: In both the groups there was a minimal but statistically significant decrease in the serum CRP levels from baseline. Previous studies [12-14] have demonstrated decrease of serum CRP levels with inhaled steroids except a study of Torres et al., [21] who reported no difference in CRP levels between patients taking steroids and those who did not. The patients of both the groups had comparable baseline characteristics and as intervention received formoterol & Budesonide with difference in treatment being addition of theophylline versus placebo in Group A and Group B respectively. Therefore any difference in outcome measures was in all probabilities due to theophylline.

Effect of Theophylline on exercise performance and lung function: Previous reports on the effect of theophylline on the exercise performance of the patients are inconsistent. Weiner et al., [22] reported a significant increase in the SMWD following therapy withlong-acting β2-agonists (LABA) plus exercise (42m) and an additional increase (50m) following therapy with LABA plus exercise plus inspiratory muscle training. In another systematic review, Liesker et al., [23] reported no significant effects of theophylline on improving exercise performance. In the present study the theophylline group showed statistically significant improvement (walked 7.94 m more) in SMWD. We noted an improvement in FEV1 of 260 ml in theophylline group, vs 210 ml in placebo group. The difference between the two groups in absolute FEV1 value and % predicted FEV1 were 50ml and 1.57% respectively - even though small but a statistically significant finding. Most of the studies done with theophylline and LABAs have demonstrated the additional advantage of theophylline in improvement of FEV1 with very few exceptions [24-26].

Effect of Theophylline on COPD symptoms: Theophylline group in present study showed more improvement in all of the symptoms, but it was more significant with respect to "Night symptoms" and "SOB on rising". Previous reports by ZuWallack et al., [25] had shown that addition of theophylline to salmeterol provided significant improvements in dyspnea, with reduced frequency of rescue medication use and fewer exacerbations than either of the agents given alone. Murciano D et al., [6] suggest that the effect of combination therapy with theophylline and LABA in COPD may go beyond bronchodilation to an improvement in various measures of patient's functional state and well being.

Mechanism of Anti inflammatory effects of Theophylline (unlocking steroid resistance): It has been proposed that the anti-inflammatory effects of theophylline could be attributed to phosphodiesterase inhibition and thus they could provide adequate bronchodilation when used in combination with β2 agonists. It is therefore not surprising that a number of studies support the combined use of theophylline and β2 agonists.The suggested molecular mechanisms by which theophylline enhances the antiinflammatory effects of steroids is mediated through HDAC2. Since, HDAC2 levels are decreased in COPD, steroids are not effective. Theophylline by virtue of HDAC2 reactivation, "unlocks" steroid resistance and allows steroids to suppress the chronic inflammation of COPD.

Adverse effects of Theophylline: The most common adverse effects observed with theophylline addition were nausea, vomiting and abdominal pain followed by palpitation, tremors headache and insomnia. The patients in the placebo group had no any significant side effects. Andrea Rossi et al., [27] in their study also observed headache, gastrointestinal intolerance, insomnia, and tremors as the most common adverse common adverse effects with theophylline. P Thomas et al., [28] study reported higher nausea scores associated with theophylline therapy and no other serious side effects. Thus the additional benefits of theophylline in COPD patients is at a cost of increase in frequency of adverse effects, not amounting to toxicity.

CONCLUSION

From the above findings it is concluded that addition of theophylline to formoterol plus budesonide is beneficial in reducing dyspnea, improving exercise performance and pulmonary function than placebo. The additional cost and increase in adverse effects involved are justified looking to the significant improvement in outcome measures. Whether a decrease in dose of theophylline will be equally effective but better tolerated needs to be studied further.

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