

## Evaluation of efficacy and safety of doxofylline 800mg sustained release tablet in treatment of patients with COPD: an open label, prospective and RCT

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**Received:** 15 January 2018

**Accepted:** 05 February 2018

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### ABSTRACT

**Background:** COPD is a major cause of health care burden worldwide and leading cause of death that is increasing in prevalence. Methylxanthines are used in the treatment of patients with asthma and COPD. Doxofylline (methylxanthine) shows improved disease control, reduced total daily dose of inhaled  $\beta_2$  agonists and improved patient compliance.

**Methods:** This was a prospective, open labelled, randomized, two-arm, parallel group, controlled, clinical trial. 115 patients were randomized to two groups. Patients in group A received tablet doxofylline 400mg BD whereas patients in group B received tablet doxofylline 800mg SR for 4 weeks. Primary outcome measure of trial was change in FEV1 and secondary outcome measure were change in FVC/FEV1, change in symptoms score, effect on health-related quality of life (HRQOL) and safety of study medication.

**Results:** At 4 week the FEV1 increase by 13.028% and 17.647% in group A and B respectively. In group A FEV1/FVC increase by 5.79% and in group B it increases by 9.57% at 4 weeks. The symptom score of cough decrease by 77.35% and 97.43% in group A and group B respectively at 4 weeks. In group A shortness of breath decrease by 77.60% and in group B it decreases by 95.90% at 4 weeks. Tightness in chest decrease by 86.29% and 98.40% in group A and group B respectively at 4 weeks.

**Conclusions:** Doxofylline 800mg sustained release tablet provided significantly greater improvement in FEV1, symptomatic control and health related quality of life compared to doxofylline 400mg.

**Keywords:** Chronic obstructive pulmonary disease, Doxofylline, Sustained release formulation

### INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease of the airways and lungs characterized by a chronic inflammatory process, in which patients develop progressive loss of lung function [e.g. fall in forced expiratory volume in first second (FEV<sub>1</sub>)] and symptoms of sputum production, leading to a reduction in quality of

life measure.<sup>1</sup> COPD is a major cause of health care burden worldwide and leading cause of death that is increasing in prevalence. COPD is recognized in 4-10% of adult male population of India and several other Asian countries.<sup>2, 3</sup> Globally, COPD by 2020, is expected to rise to the 3<sup>rd</sup> position as a cause of death and at 5<sup>th</sup> position as a cause of loss of disability adjusted life years (DALYs) according

to the baseline projections made in the Global Burden of Disease Study (GBDS).<sup>3</sup>

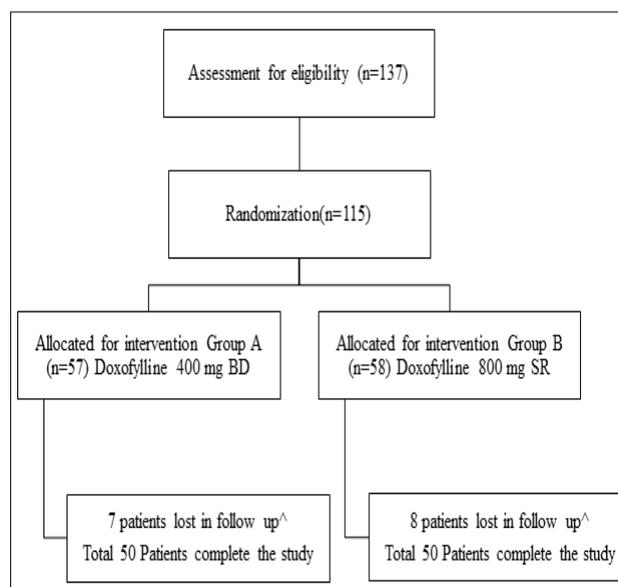
Prevention of disease progression, improvement of symptoms and exercise tolerance and decrease in exacerbations and mortality are the goals of management.<sup>4</sup> Drugs including short and long acting bronchodilators, anti-cholinergic, methylxanthines, and corticosteroids, are used as single agents or in combination to treat patients with COPD.<sup>2</sup> Methylxanthines are a group of structurally related compounds that are widely used in the treatment of patients with asthma and COPD. Methylxanthines are beneficial in chronic management and maintenance of obstructive lung diseases. They can be added to patient's regimen if inhaled agents fail to control the disorder.<sup>5,6</sup> Doxofylline (Methylxanthine) having favourable profile, most notably because of no reports of fatal events or major arrhythmias and no effect on sleep architecture.<sup>5,7</sup> Sustained release once daily formulation of methylxanthines was associated with improved disease control, reduced total daily dose of inhaled  $\beta_2$  agonists and improved patient compliance.<sup>8,9</sup> To extend the benefits offered by doxofylline and considering the beneficial effects of once daily formulations the present trial planned to evaluate the efficacy and effect on quality of life with doxofylline sustained release formulation in patients with COPD.

## METHODS

This was a prospective, open labelled, randomized, two-arm, parallel group clinical trial. It was conducted in compliance with the protocol, after Institutional Ethics Committee (IEC) approval, informed consent regulations, as per Declaration of Helsinki, ICH good Clinical Practice (GCP) guidelines and the ICMR guidelines for Biomedical Research on Human Subjects, 2006. COPD patients attending the outpatient department (O.P.D.) of medicine of a tertiary health care centre in Aurangabad were recruited in trial. Patients of either gender between 18 to 55 years of age with COPD stable on medication, as diagnosed by the physician, were included in the trial. All patients provided written, vernacular, witnessed, informed consent to participate in the trial. Patients with severe COPD requiring oxygen therapy, COPD exacerbation in the 4 weeks prior to screening visit or untreated serious respiratory tract infectious disease were not included in trial. Patient with history of hypersensitivity to study medication, history of asthma, allergic rhinitis, atopy, or an elevated blood eosinophils count were excluded from the trial. Patient with moderate to severe cardiac disease, severe renal or hepatic disease, active peptic ulcer disease were also excluded from trial and pregnant or breastfeeding females were not included in trial.

All patients willing to participate and give an informed written consent were screened for eligibility. Baseline evaluation included recording of demographic details, medical history, general and systemic examination. The investigations were carried out at the beginning of the

study (screening visit) to rule out any serious medical illness and again repeated at the end of treatment period to assess safety of the study drug. Other tests included were Spirometry at the baseline and 4 week, X-ray Chest (PA view) and ECG only at screening visit. During washout phase (run-in phase) all methylxanthines (theophylline and doxofylline) and all beverages containing xanthines were withheld from all patients. After the run-in phase of 1 week the eligible patients were enrolled and randomized, by a computer generated randomization sequence, into two treatment groups. Patients in Group A received doxofylline 400mg two times in a day (BD) and patients in group B received doxofylline 800mg sustained release (SR) once in a day (OD) for 4-weeks. Patients were evaluated at baseline and 4 weeks. (Figure 1).



**Figure 1: The run-in of intervention.**

These patients were lost to trial because of abnormal laboratory parameters or when some patients started taking concurrent medications or patients from remote area who did not report for follow up.

The clinical efficacy was evaluated based on subjective and objective parameters. Changed in the FEV1 and FVC were assessed at the baseline and 4 week by spirometry. The symptoms score was assessed as follows: 0 = no symptoms, 1 = symptoms, but not affecting any activities during day/sleep at night, 2 = symptoms affecting at least one activity or disturbing sleep, 3 = symptoms affecting >2 daily activities or disturbing sleep all night or most on the night. Impact of the treatment on health related quality of life (HRQOL) was evaluated by using St. George's Respiratory Questionnaire for COPD patients (SGRQ-C). Component of SGRQ-C are symptom, activity, impact score and total score. Higher scores indicating poor quality of life and decrease in scores indicating improvement in the same. Primary outcome measure of trial was change in FEV1 and secondary outcome measure were change in FVC/FEV1, change in symptoms score, effect on health

related quality of life (HRQOL) and safety of study medication.

### Statistical analysis

All the data was entered into Microsoft Excel from case record form for analysis. For comparing quantitative data within the study groups Students Paired 't' test was used

and for comparing quantitative data between the study groups Students Unpaired 't' test was applied. Comparison of qualitative data between the study groups was done using Fisher's exact test. Statistical analysis was performed with the help of the software 'Graph pad Prism 5'. The p value of <0.05 was considered as statistically significant. SGRQ component Score and total score analysed by SGQR Excel-based scoring calculator.

**Table 1: Baseline characteristics in study groups.**

| Parameter          | Group A (n=50) Doxo 400mg BD | Group B (n=50) Doxo 800mg SR | 'P' value           |
|--------------------|------------------------------|------------------------------|---------------------|
| Age in years       | 54.96±0.926                  | 56.16±0.805                  | 0.3306 <sup>†</sup> |
| Gender             | Men (n)                      | 35                           | 0.8240 <sup>‡</sup> |
|                    | Women (n)                    | 15                           |                     |
| Height (cm)        | 158.6±3.061                  | 161.2±0.889                  | 0.4275 <sup>†</sup> |
| Weight (Kg)        | 53.88±0.613                  | 53.76±0.593                  | 0.8885 <sup>†</sup> |
| Smoker             | 34                           | 35                           | 1.0000 <sup>†</sup> |
| ECG (QTc interval) | 0.38±0.02                    | 0.37±0.02                    |                     |

[Doxo: doxofylline, SR: Sustained release; n: Numbers; Values: Mean±SD (otherwise mentioned); †: Using 2-tailed unpaired t-test, ‡: Using Fisher's exact test; \*: Statistically significant (P <0.05)]

**Table 2: Assessment of efficacy parameter.**

| Parameter                         | Group A (n=50) Doxo 400mg BD | Group B (n=50) Doxo 800mg SR | P value inter group <sup>†</sup> |
|-----------------------------------|------------------------------|------------------------------|----------------------------------|
| Mean FEV1 (% predicted)           |                              |                              |                                  |
| Baseline                          | 46.36±0.954                  | 46.10±0.920                  | 0.8450                           |
| 4 Weeks                           | 52.40±0.777                  | 54.80±0.725                  | 0.0262*                          |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Mean FVC (% predicted)            |                              |                              |                                  |
| Baseline                          | 51.24±0.944                  | 51.18±0.981                  | 0.9650                           |
| 4 Weeks                           | 54.64±1.059                  | 55.98±1.025                  | 0.3654                           |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Mean FEV1/FVC                     |                              |                              |                                  |
| Baseline                          | 97.04±1.425                  | 96.98±1.403                  | 0.9761                           |
| 4 Weeks                           | 102.7±1.188                  | 106.2±1.175                  | 0.0346*                          |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Mean score of Cough               |                              |                              |                                  |
| Baseline                          | 2.340±0.083                  | 2.340±0.088                  | 1.0000                           |
| 4 Weeks                           | 0.580±0.131                  | 0.060±0.033                  | 0.0002*                          |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Mean score of shortness of breath |                              |                              |                                  |
| Baseline                          | 2.500±0.095                  | 2.440±0.099                  | 0.6652                           |
| 4 Weeks                           | 0.360±0.089                  | 0.100±0.042                  | 0.0100*                          |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Mean score of Chest tightness     |                              |                              |                                  |
| Baseline                          | 2.400±0.221                  | 2.500±0.095                  | 0.6793                           |
| 4 Weeks                           | 1.020±0.108                  | 0.040±0.027                  | <0.0001*                         |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Symptoms free days in weeks       |                              |                              |                                  |
| Baseline                          | 1.900±0.266                  | 1.980±0.256                  | 0.8293                           |
| 4 Weeks                           | 6.040±0.249                  | 6.880±0.067                  | 0.0016*                          |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |
| Symptoms free night in weeks      |                              |                              |                                  |
| Baseline                          | 1.660±0.248                  | 1.560±0.265                  | 0.7838                           |
| 4 Weeks                           | 5.820±0.280                  | 6.800±0.0857                 | 0.0012*                          |
| P value intragroup <sup>§</sup>   | <0.0001*                     | <0.0001*                     |                                  |

[Doxo: Doxofylline; SR: Sustained release; n: Numbers; Values: Mean±SEM (otherwise mentioned); FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; FEV<sub>1</sub>/FVC- ratio of forced expiratory volume in one second and forced vital capacity; †: Using 2-tailed unpaired t-test; ‡: Using Fisher's exact test; §: Using paired t-test; \*: Statistically significant (P <0.05)]

## RESULTS

Total of 137 patients with COPD were screened, and 115 eligible patients were randomized into two treatment groups. In group A 7 patients and in group B 8 patients were lost to trial. Both groups were similar in all baseline parameters at the start of study, as shown in Table 1.

Findings of the study are as discussed below taking into account inter-group and intra-group comparison. (Table 2). At 4 week the mean value of FEV1 increase by 13.028% and 17.647% in group A and B respectively from baseline which was statistically significant in both groups. In group A FEV1/FVC increase by 5.79% and in group B it increases by 9.57% at 4 week from baseline which was statistically significant. At 4 week the symptom score of cough decrease by 77.35% and 97.43% in group A and group B respectively from baseline. In group A shortness of breath decrease by 77.60% and in group B it decreases by 95.90% at 4 week from baseline. At 4-week tightness in chest decrease by 86.29% and 98.40% in group A and group B respectively. At 4 week the symptom free days increase by 4.14 and 4.90 in group A and B respectively from baseline and symptom free night increase by 4.16 and 5.24 in group A and B respectively from baseline (Table 2).

**Table 3: Assessment of St. George's respiratory questionnaire for COPD patients.**

| Parameter                          | Group A<br>(n=50)<br>Doxo<br>400mg BD | Group B<br>(n=50)<br>Doxo<br>800mg SR | P value<br>inter<br>group <sup>†</sup> |
|------------------------------------|---------------------------------------|---------------------------------------|--|
| <b>SGRQ Symptom score</b>          |                                       |                                       |  |
| Baseline                           | 84.13±0.944                           | 84.33±0.936                           | 0.8838                                 |
| 4 Weeks                            | 61.02±2.798                           | 45.78±1.895                           | <0.0001*                               |
| P value<br>intragroup <sup>§</sup> | <0.0001*                              | <0.0001*                              |  |
| <b>SGRQ Activity score</b>         |                                       |                                       |  |
| Baseline                           | 77.92±0.279                           | 77.82±0.273                           | 0.7917                                 |
| 4 Weeks                            | 52.98±3.567                           | 38.92±2.244                           | 0.0012*                                |
| P value<br>intragroup <sup>§</sup> | <0.0001*                              | <0.0001*                              |  |
| <b>SGRQ Impact score</b>           |                                       |                                       |  |
| Baseline                           | 79.95±0.326                           | 80.04±0.328                           | 0.8481                                 |
| 4 Weeks                            | 61.41±2.479                           | 46.70±1.715                           | <0.0001*                               |
| P value<br>intragroup <sup>§</sup> | <0.0001*                              | <0.0001*                              |  |
| <b>SGRQ Total score</b>            |                                       |                                       |  |
| Baseline                           | 85.89±0.351                           | 85.87±0.324                           | 0.9631                                 |
| 4 weeks                            | 61.80±3.330                           | 44.15±2.591                           | <0.0001*                               |
| P value<br>intragroup <sup>§</sup> | <0.0001*                              | <0.0001*                              |  |

[Doxo: Doxofylline; SR: Sustained release; n: Numbers; Values: Mean±SEM (otherwise mentioned); †: Using 2-tailed unpaired t-test; ‡: Using Fisher's exact test; §: Using paired t-test; \*: Statistically significant (P <0.05); SGRQ: St. George's Respiratory Questionnaire for COPD patients]

The SGRQ symptom score were decrease by 27.51% in group A and 45.74% in group B at 4 week. The SGRQ activity score were decrease by 37.06% and 59.18% in group A and B respectively at 4 week. The SGRQ total score were decrease by 28.04% in group A and 48.77% in group B at 4 week (Table 3).

## DISCUSSION

COPD is one of the leading problems affecting majority of population all over the world, which diminishes the quality of life of the individual and creates extra burden to the society.<sup>4,10</sup>

GOLD guidelines emphasize that methylxanthines are effective in COPD.<sup>11,12</sup> They decreases the overall resistance of the airways, improves blood gas exchange and reduces dyspnea.<sup>13,14</sup> Doxofylline not only a bronchodilator but also reduce inflammatory changes and altered cell proliferation of the bronchial wall.<sup>15,16</sup> Doxofylline has been effective in the improvement of FEV1, vital capacity and PEF and reduces the rate of exacerbations.<sup>17,18</sup>

The once daily sustained release formulation of methylxanthines has shown to benefit patients in terms of better control of their disease activity and improved compliance in obstructive lung disease.<sup>8,9</sup>

In the present study, doxofylline 800mg SR OD was compared with doxofylline 400mg BD in the stable chronic obstructive pulmonary disease patients. The results of present study showed significant improvement in mean values of FEV1 at 4 weeks in both the study groups, in intergroup comparison, the response being significant with doxofylline 800 mg SR group.

Moreover, when compared with other parameters of spirometry, the mean values of FVC and FEV1/FVC showed significant increase at 4 weeks in both groups, in the inter group comparison FEV1/FVC difference was significant in doxofylline 800 mg SR group. These findings are in accordance with those in studies carried out by Dini et al, Mirabelli et al, and Villani et al.<sup>14,19,20</sup>

The present study found significant improvement in symptomatic control in both groups in terms of reduction in symptom score [cough, shortness of breath, chest tightness]. Intergroup comparison showed a statistically significant difference between the two groups, symptom control being better with doxofylline 800mg SR group. The current study found increase in symptom free days and nights in both groups and the difference was significant with doxofylline 800mg SR group.

The current study found that the SGRQ-C scores showed significant decrease from baseline after treatment in both study groups. Improvement in quality of life was significant with doxofylline 800mg SR group in comparison with doxofylline 400mg group. The number of

patients experiencing study drug related adverse effects was comparable between doxofylline 800mg SR and doxofylline 400mg BD groups and they were self-limiting. No serious adverse effects were reported in any of study groups and not a single patient was withdrawal due to adverse effects. These findings were in accordance with studies carried by Kurli et al, Goldstein et al and Sankar et al.<sup>11,21,22</sup>

## CONCLUSION

Doxofylline 800mg SR OD and doxofylline 400mg BD showed significant improvement in efficacy measures in patients with COPD. But doxofylline 800mg SR OD provided significantly greater improvement in FEV1, symptomatic control and health related quality of life compared to doxofylline 400mg BD. Thus, doxofylline 800 mg sustained release formulation, single dose, can be considered as a better treatment option in patients suffering from COPD.

## ACKNOWLEDGEMENTS

Authors are grateful to all the staff members of Department of Medicine, Government Medical College and Hospital Aurangabad, for their valuable cooperation.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Khandelwal PN, Maaz SH, Borade DM. Evaluation of efficacy and safety of doxofylline 800mg sustained release tablet in treatment of patients with COPD: an open label, prospective and RCT. *Int J Basic Clin Pharmacol* 2018;7:644-9.