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OPEN LABELLED RANDOMIZED PROSPECTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE AND THEOPHYLLINE IN COPD PATIENTS

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ABSTRACT:

OBJECTIVE:

To compare the safety and efficacy of oral doxofylline with theophylline in Grade 1-2 COPD patients at baseline and after 6 weeks .

MATERIALS AND METHODS

STUDY DESIGN:

Randomised, Comparative, Open label, Single centre, Prospective Parallel group Study.

STUDY CENTRE:

Department of Chest Medicine in Tirunelveli Medical College Hospital.

STUDY POPULATION:

Grade1-2 COPD patients (Based on GOLD Criteria) attending the outpatient department of Chest Medicine in Tirunelveli Medical College Hospital

CONCLUSION

Based on the results of this we conclude that,

- Doxofylline is found to be equally efficacious when compared to theophylline in the treatment of Grade 1-2 COPD(GOLD Criteria).
- Doxofylline has a better safety and tolerability profile when compared to theophylline.
- Doxofylline would offer an equivalent and safer alternative to theophylline in the management of COPD.

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- Since this study was done in a small group ,conformation of this result has to be done with a study using larger sample size.

INTRODUCTION

COPD is an important public health problem which is preventable as well as treatable. It is one of the major cause of chronic morbidity and mortality throughout the world. It is the fourth leading cause of death[1].

COPD has been defined by The Global Initiative for Obstructive Lung Disease [2] (GOLD) as a disease state characterized by airflow limitation that is not fully reversible. Theophylline is used as a bronchodilator in the pharmacotherapy of COPD for many decades. Due to its narrow therapeutic index, the plasma concentration of therapeutic range was maintained at 10 to 20 mg/L. Theophylline has anti-inflammatory effects on small airways and reduction of hyperinflation leading to reduction in dyspnea. The proposed mechanisms of action of Theophylline are Nonselective Phosphodiesterase inhibition, stimulation of epinephrine release, Adenosine receptor antagonism, increased interleukin-10 release, inhibition of mediators (prostaglandins, tumor necrosis factor), inhibition of nuclear factor-κB, increased apoptosis, inhibition of intracellular calcium release and increased histone deacetylase activity[3].

Doxofylline is a newer xanthine bronchodilator that differs from theophylline. Doxofylline has a dioxalane group in position-7. Similar to theophylline its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it has decreased affinity towards adenosine A1 and adenosine A2 receptors. The bronchodilation effect of doxofylline has been demonstrated in bronchial asthma and chronic obstructive pulmonary disease clinical trials. Contrary to other bronchodilators, experimental and clinical studies has shown that doxofylline is devoid of stimulatory effects. The arrhythmogenic action of bronchodilators have negative impact on the morbidity and mortality of patients with respiratory diseases which is devoid in doxofylline usage. The unique cardiovascular safety profile of doxofylline makes it unnecessary to monitor the serum levels of the drug.

Although doxofylline shares most of the characteristics of the methylxanthine drugs, experimental studies has shown that it is associated with less extra-respiratory effects than theophylline[4,5,6].

Though few previous studies have advocated the efficacy and safety of doxofylline over theophylline, the comparison of the clinical efficacy and safety profile of doxofylline with theophylline in the Indian population has been less studied. Therefore, the present study is designed to compare the clinical efficacy and safety of oral theophylline and doxofylline in patients with Grade1-2 COPD (Based on GOLD Criteria) attending the outpatient department of Chest Medicine in Tirunelveli Medical College Hospital.

AIM OF THE STUDY

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To compare the safety and efficacy of oral doxofylline with theophylline in Grade 1-2 COPD patients.

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STUDY PERIOD:

One Year from April 2021 to March 2022

INCLUSION CRITERIA:

1. All the stable patients who were diagnosed clinically with COPD by the outpatient department of the hospital were enlisted and those having FEV1 within 50% to 80% of the predicted FEV1 for their age and height and showed non reversibility of FEV/FVC<70% Value, 20 minutes after inhalation of two puffs (400 microgram) of salbutamol are taken up for the study.

2. Adults, 18 years of age and above. Irrespective of gender.

3. Patients who have given written informed consent to participate in the study.

EXCLUSION CRITERIA:

1. Clinically significant cardiovascular diseases, including a history of congestive cardiac failure, angina pectoris within previous 1 year.

2. Convulsive disorders.

3. Clinical significant gastro-intestinal diseases including active peptic ulcers within preceding 1 year.

4. Renal diseases, hepatic diseases, and hematologic diseases

5. Known infection with human immunodeficiency virus.

6. Presence of any acute illness.

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7. Sensitivity to theophylline or theophylline like agents.

8. Pregnant and Lactating women.

9. Patients on warfarin and digoxin.

SAMPLE SIZE:

60(each group – 30)

METHODOLOGY:

This is an open study, and patients will be enrolled after written informed consent as per the inclusion and exclusion criteria. For all patients, their current medical history and Diagnosis, COPD Grade will be noted. Detailed medical history with general and systemic examination will be done. All the baseline investigations, Hemoglobin, total leucocyte count, differential leucocyte count, liver function tests, kidney function tests will be done. Pulmonary function test (spirometry) assessments, COPD Assessment Test (CAT) Questionnaire assessment will be performed for every patient. Demographic data will be collected from all the patients. After enrollment, each group will be randomized using computerized randomized tables and divided into two subgroups.

Group I patients will be administered Theophylline, 100 mg thrice daily and group II patients will be administered doxofylline 400 mg twice daily, orally for a duration of 6 weeks. Both Group I and Group II patients will be on oral short acting beta 2 agonist salbutamol 4 mg BD. Follow up visits will be at 6 weeks .

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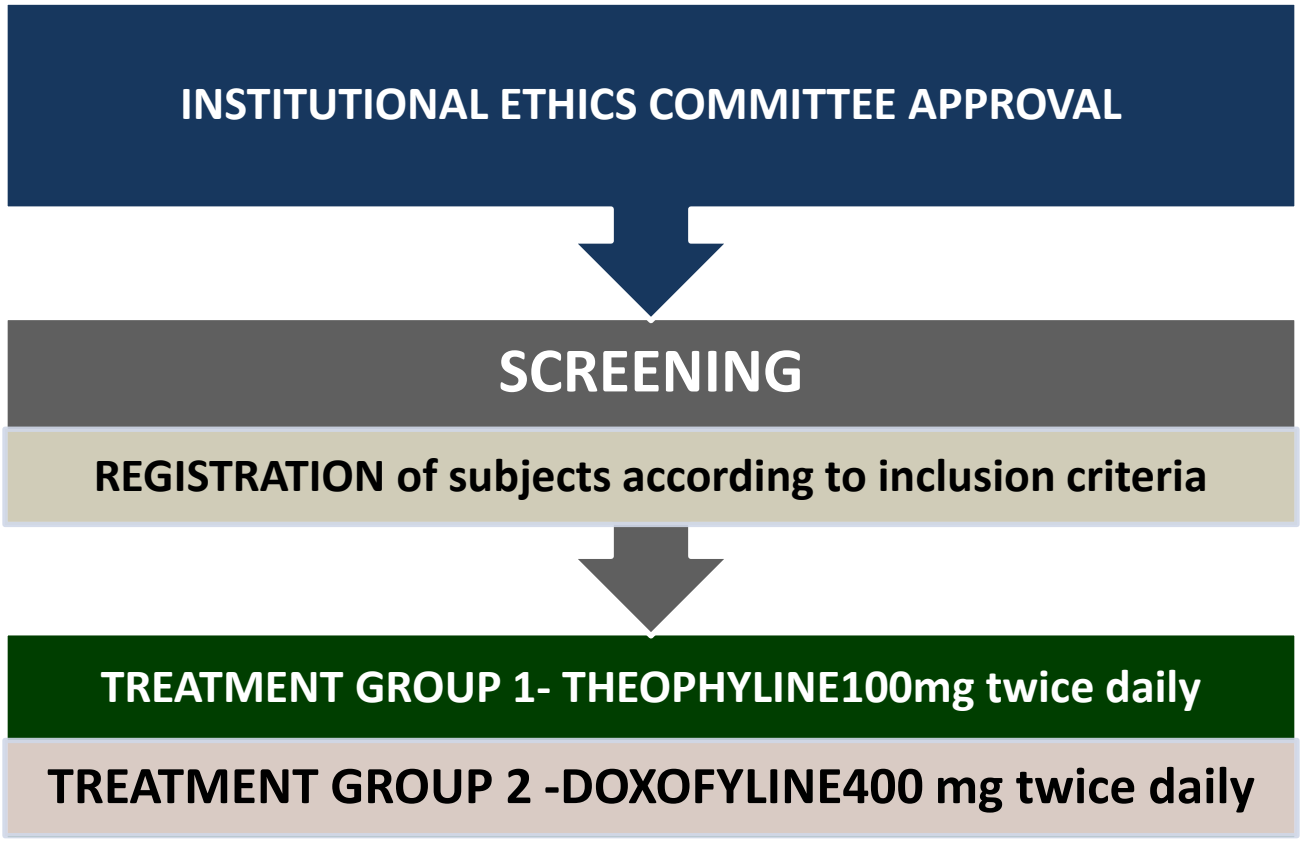

RESULTS

Table - 1

COMPARISON OF FEV1 AND FVC FROM BASELINE TO 6 WEEKS IN DOXOFYLLINE GROUP (WITHIN GROUP)

Variables	VISITS	Mean	Std. Deviation	Mean difference	P value
FEV1	BASELINE	58.9000	20.09118	–	–
	6 WEEKS	67.1000	15.97533	-8.200	0.086
	BASELINE	76.3000	22.63748	–	–

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Variables	VISITS	Mean	Std. Deviation	Mean difference	P value
FEV1	BASELINE	58.9000	20.09118	–	–
	6 WEEKS	67.1000	15.97533	-8.200	0.086
FVC					
	6 WEEKS	88.0000	27.27636	-11.700	0.231

Table 1 : shows the mean and standard variation of FEV1and FVC for doxofylline group and it shows statistically significant improvement from baseline to 6 weeks

COMPARISON OF ADVERSE EFFECTS OBSERVED BETWEEN DOXOFYLLINE AND THEOPHYLLINE GROUP PATIENTS

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Figure 1

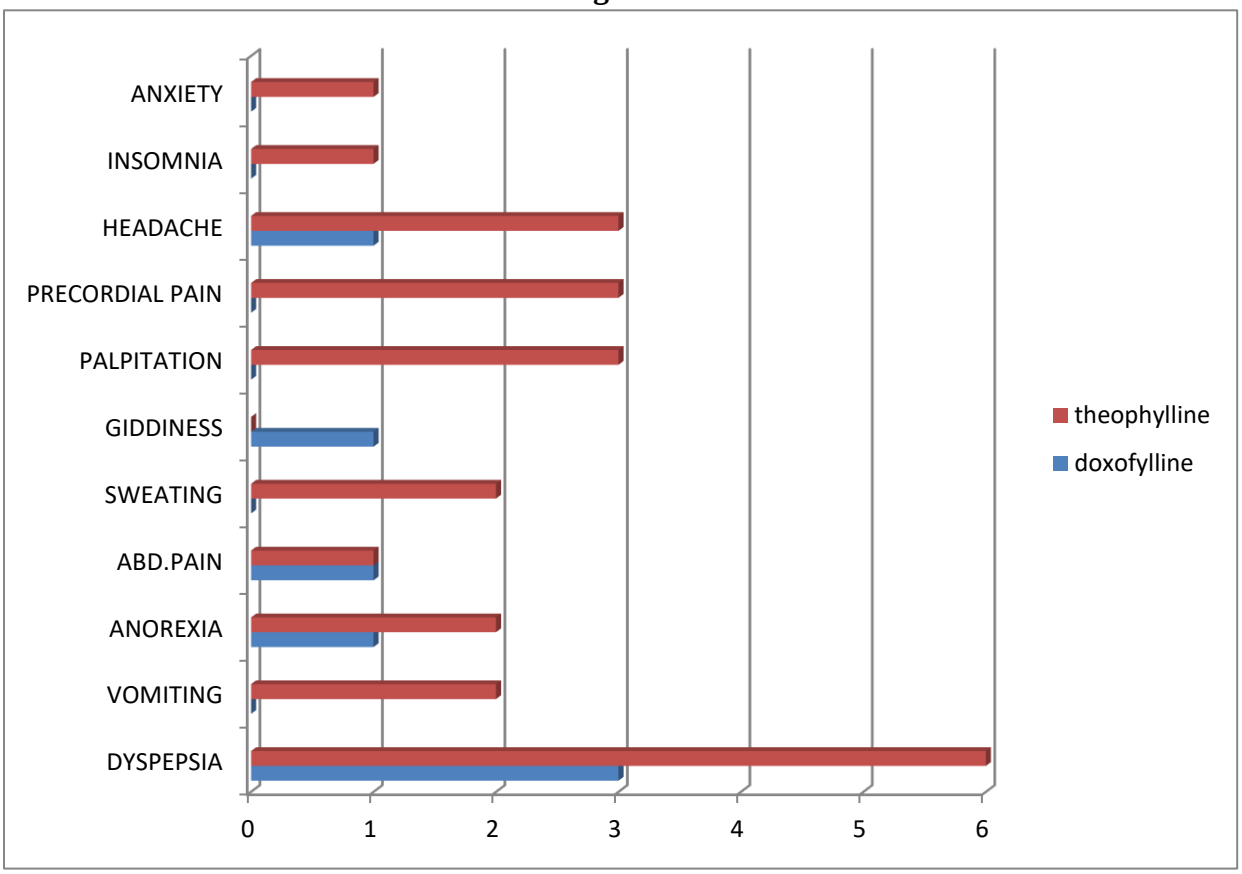

Figure 1: shows the total number of patients who reported adverse drug events in both doxofylline and theophylline group . The number of ADR in theophylline group is higher compared with doxofylline group patients. The most common adverse effect observed in both groups was dyspepsia.

DISCUSSION

Obstructive diseases of the airways are characterized by an increase in resistance to airflow ranging from partial to complete obstruction at any level, from the trachea and larger bronchi to the terminal and respiratory bronchioles. The major obstructive disorders are COPD (emphysema and chronic bronchitis) and bronchial asthma[7].

The comparison of the clinical efficacy and safety profile of doxofylline with theophylline in the Indian population was less studied. The present study was designed to compare the clinical efficacy

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and safety of oral theophylline and doxofylline in patients with Grade1-2 COPD (Based on GOLD Criteria).

Diagnosis of COPD is made on clinical judgment based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using lung function testing (spirometry). Spirometry provides objective information about pulmonary functions and assesses the result of therapy

Bronchodilators are the main stay in the treatment option for symptom relief in COPD. Methylxanthines are emerging as effective option in the treatment of obstructive airway diseases and drugs such as theophylline and doxofylline have been used orally in these disorders.

Doxofylline is a newer xanthine bronchodilator that differs from theophylline. Although doxofylline shares most of the characteristics of the methylxanthine drugs, experimental studies has shown that it is associated with less extra-respiratory effects than theophylline[3,4,5].

Spirometric parameters were assessed at the start of the study .The mean FEV1 value for doxofylline group was 58.9±20.09 and for theophylline group, it was 53.3±29.39.The mean FVC value for doxofylline group was 76.3±22.63 and for theophylline group it was 76.5±23.17.the mean FEV1/FVC value for doxofylline group was 75±13.59 and for theophylline group it was 65.8±14.69.

At the end of our study, when the spirometric assessment was compared between the two treatment groups, the mean value of FEV1 in doxofylline group was 74±15.54 compared with mean value of FEV1 of theophylline group which was 68.6±36.65

CONCLUSION

Based on the results of this we would say that,

- Doxofylline is found to be equally efficacious when compared to theophylline in the treatment of Grade 1-2 COPD (GOLD Criteria).
- Doxofylline has a better safety and tolerability profile when compared to theophylline.
- Doxofylline would offer an equivalent and safer alternative to theophylline in the management of COPD.
- Since this study was done in a small group ,conformation of this result has to be done with a study using larger sample size.

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