Original article

Comparison of Effectiveness of Doxofylline VS Theophylline in Stable Chronic Obstructive Pulmonary Disease Patients

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is known as an obstructive pulmonary disease it causes particular small airway obstruction. Currently available medications for COPD are not able to reduce the progressive deterioration of lung function. The current study aims to determine the effectiveness of doxofylline and theophylline in improving the pulmonary functions in stable COPD patients.

Methods: A Randomized controlled trial was conducted on a total of 80(40 in each group). Stable COPD patients (FEV1/FVC < 0.70) patients visiting the outpatient department of Sir Ganga Ram Hospital for treatment and fulfilling inclusion criteria were enrolled to participate in the study. Both groups were given standard long-acting bronchodilator therapy such as salmeterol inhaler 25mcg twice daily. Group A was given theophylline, while group B was given doxofylline. Independent sample t-test was applied to compare the spirometry findings in both groups by using SPSS 25.0. A p-value of ≤0.05 was considered statistically significant.

Results: In current study it was reported that the 36 (45.0) of patients were 30-40 years old. The majority of patients were male 68(85.0%) and suffered from COPD. There was an increased improvement in spirometric parameters among both groups. The both groups have same effect on spirometric parameters in terms of FEV1, FVC, FEV1/FVC and FEC1% prediction. Both drugs increase the spirometry functionality. (p-value > 0.05). There was significant difference among side effect of both groups. Doxophylline was found to have fewer side effects compared to theophylline. (P value< 0.05)

Conclusion: It was concluded that the both drugs theophylline and doxofylline revealed consistent improvement in spirometric outcomes (FEV1, FVC, and the FEV1/FVC ratio) with the passage of time in COPD. The current study demonstrates that both drugs have a equal efficacy and safety profile than theophylline in patients with COPD.

Keywords:

Chronic Obstructed pulmonary disease, Effectiveness, Theophylline, Doxofylline, Spirometery

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a multicomponent, preventable, treatable, chronic non-partial inflammatory, respiratory disease manifested outside the lung parenchyma [1]. It is associated with exacerbations and stressful conditions that increases the total disease severity field[2]. It causes particular small airway obstruction, which leads to structural problems such as the constriction of the airways due to lung parenchyma and obstructive bronchiolitis[3,4]. Around the world, COPD is considered to be the leading cause of mortality. According to a study by the Global Burden of Disease (GBD), its prevalence is growing rapidly and it is estimated that it will be the 3rd leading cause of mortality in developing countries till in the year 2030[5]. The results of the "Breathe Study" reported the prevalence of COPD in Pakistan for men at 3.3% and for women at 0.8%[6]. Due to the increasing number of drugs available for treating COPD, it has become increasingly difficult to determine the potential risks and benefits of different treatment methods. The use of xanthine derivatives such as theophylline and doxofylline is contradictory[7]. Another type of xanthine derivatives that are commonly used for treating COPD is doxofylline. It has a favourable risk-to-benefit ratio and a similar efficacy as theophylline[8–10]. Stable COPD patients use oral xanthine derivatives (like theophylline and doxofylline) to ease symptoms, enhance exercise tolerance, and prevent exacerbations, but no medication has been proven to reduce COPD mortality. According to the literature, doxofylline is a more effective bronchodilator than theophylline and has a better safety profile[11]. However, doxofylline is yet not recommended in any guideline for management of COPD. Therefore, this study was conducted to determine the role of doxofylline and theophylline in stable COPD patients.

METHODS

A Randomized controlled trial was conducted on a total of 80 patients (40 in each group). Stable COPD

Conflict of interest: The authors declared no conflict of interest exists.
Citation: Raza A, Ramzan Z, Khalid AR, Rehman A, Sultan I, Afzal MA. Comparison of Effectiveness of Doxofylline VS Theophylline in Stable Chronic Obstructive Pulmonary Disease Patients. J Fatima Jinnah Med Univ. 2023; 17(1):07-10.

DOI: https://doi.org/10.37018/DZDU6498

(FEV1/FVC < 0.70) patients visiting the outpatient department of Sir Ganga Ram Hospital for treatment and fulfilling inclusion criteria were enrolled to participate in the study. The patients were randomly allocated into two equal groups (1:1) using a randomized block. Both groups were given standard long-acting bronchodilator therapy such as salmeterol inhaler 25mcg twice daily. Group A was given theophylline (300mg once a day orally) while group B was given doxofylline (400mg twice a day orally). The subjects were followed up after 4 and 6 weeks for clinical/subjective improvement and spirometry was performed. In case of worsening symptoms, the patient was offered admission to the ward for treatment.

All the data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Independent sample t-test was applied to compare spirometry values in both groups. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The mean age of patients in theophylline was 48.75±14.1vs doxofylline was 46.56±15.4 with insignificant difference (P-value >0.05). There were 40 patients in the theophylline group [F=12(30.0) Vs. M=28(70.0), P-value >0.05] and 40 patients in the doxofylline group [F=8(20.0) Vs. M=32(80.0), P-value >0.05]. The majority of patients had a normal BMI. The comparison of the stages of COPD showed that the 42 have mild COPD, including 31 in the theophylline group and 11 in the doxofylline group (Table 1)

Table 1: Baseline Characteristics of patients

Variables	Theophylline (n =40)	Doxofylline (n =40)	P-value
Age (Mean±SD)	48.75±14.1	46.56±15.4	0.95
	Gender		
Female	12(30.0%)	8(20.0%)	0.302
Male	28(70.0%)	32(80.0%)	
	BMI		
Underweight	4(10.0%)	4(10.0%)	0.877
Normal	24(60.0%)	26(65.0%)	
Overweight	12(30.0%)	10(25.0%)	
	Smoking Packs per year		
10-20 packs	28(70.0%)	18(45.0%)	0.143
21-30 packs	6(15.0%)	10(25.0%)	
31-40 packs	6(15.0)	12(30.0%)	
	Gold stage of COPD		
Mild	31(77.5%)	11(27.5%)	0.000
Moderate	4(10.0%)	9(22.5%)	
Severe	4(10.0%)	15(37.5%)	
Very Severe	1(2.5%)	5(12.5%)	

Table 2: Comparison of Spirometric parameters among groups at 4th and 6th week Independent Sample t test

Spirometric parameters	Follow ups	Theophylline (n=40)	Doxofylline (n=40)	t-value	*P-value*
FEV_1	**Baseline**	2.09±0.38	2.07±0.44	-2.96	0.786
	At 4 Week	2.08±0.39	2.09±0.44	-0.083	0.934
	At 6 Week	2.1±0.39	2.11±0.43	0.03	0.998
FVC	**Baseline**	2.99±0.49	3.05±0.56	-0.422	0.674
	At 4 Week	3.0±0.48	3.10±0.55	5.41	0.71
	At 6 Week	3.0±0.48	3.06±0.55	-0.49	0.64
FEV_1/FVC	**Baseline**	65.7±7.09	65.8±6.98	0.79	0.937
	At 4 Week	66.9±7.80	66.2±7.08	0.42	0.676
	At 6 Week	67.5±8.01	67.0±7.19	0.455	0.650

Table 3: Comparison of Side effect among groups

Side Effects	Theophylline (n=40)	Doxofylline (n=40)	Total
Nausea	15(75.0)	5(25.0)	20
Vomiting	6(85.7)	1(14.3)	7
Abdominal Pain	4(80.0)	1(20.0)	5
Dyspepsia	15(71.4)	6(28.60	21
Headache	15(57.7)	11(42.3)	26
Anorexia	4(80.0)	1(20.0%)	5
Sweating	5(100.0)	0(0.0)	5
Palpitation	7(77.8%)	2(22.2)	9
Mean value of side effect	8.875±5.16	3.375±3.7	
P Value		0.000	

Table 4.3 shows the spirometry finding among both groups at baseline, 4th and 6th week of study. The FEV_1 at baseline, 4th and 6th week in theophylline group was 2.09±0.38, 2.08±0.39 and 2.1±0.39 as compared to doxofylline group was 2.07±0.44, 2.09±0.4 and 2.11±0.43. The FVC at baseline, 4th and 6th week in theophylline group was 2.99±0.49, 3.0±0.48 and 3.0±0.48 as compared to doxofylline group was 3.05±0.56, 3.10±0.55 and 3.06±0.55. The FEV_1/FVC at baseline, 4th and 6th week in theophylline group was 65.7±7.09, 66.9+7.80 and 67.8+8.01 as compared to doxofylline group was 65.8±6.98, 66.2±7.08 and 67.0+7.19. There was an improvement in spirometric parameters among both groups. The independent sample t test showed that the both groups have same effect on spirometric parameters in terms of FEV1, FVC, and FEV1/FVC prediction. Both drugs increase the spirometry functionality (p-value> 0.05)

The most common side effects observed were headache, dyspepsia, and nausea. Compared to side effects, the most common side effect was headache (Theophylline= 15(57.7) Vs. Doxofylline =11(42.3)], followed by dyspepsia [(Theophylline= 15(71.4)Vs. Doxofylline =6(28.60)] and nausea [(Theophylline= 15(75.0) Vs. Doxofylline =5(25.0)). Palpitations were reported by 9 patients [(theophylline= 7(77.8%)Vs. Doxofylline =2(22.2)). Sweating was reported by only 5 patients in the theophylline group. There was

significant difference among side effect of both groups. Doxophylline was found to have fewer side effects compared to theophylline. (P value< 0.05). (Table 3)

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is one of the world's most serious public health issues. COPD is the world's seventh largest cause of mortality and disability[12]. For decades, theophylline has been primarily used to treat COPD patients. A novel theophylline congener, doxofylline, is said to have a superior safety profile. Therefore, this study was conducted to compare efficacy of doxofylline and theophylline in stable chronic obstructive pulmonary disease patients via spirometery.

In current study it was reported that the majority of patients were more than 30 years old with majority male patients with COPD.A study conducted on gender biasness in the diagnosis of COPD showed that the COPD was initially reported as the most likely diagnosis more often in men than in women (58 percent vs. 42 percent; p 0.05). After spirometery, COPD diagnosis rates were 74 % and 66 % in men and women, respectively. These findings were similar with current study which reveals than COPD is more prevalent in males[13].

In our study, both medicines were effective in improving the spirometric parameters in stable COPD patients with statistically insignificant difference.

In a study with 346 patients randomly assigned to two groups and tracked for 12 weeks, doxofylline exhibited a significant FEV1 increase compared to theophylline. Similar effects were noted in lung function tests (FVC, PFER, FEV1/FVC ratio). These findings align with the current study, demonstrating improved spirometry in COPD patients treated with theophylline and doxofylline. Notably, doxofylline led to a substantial 208ml increase in FEV1, while theophylline showed a 136ml increase from their respective baselines[14].

Review of literature suggests that doxofylline is an effective bronchodilator and displays a better safety profile than theophylline[15]. The most common side effects in our study included headache, dyspepsia, and nausea. Headache was the most common side effect. There was a significant difference in side effects between groups, with doxofylline having fewer adverse effects than theophylline (P < 0.05).

Studies have reported wider therapeutic window for doxofylline than theophylline. It also has anti-inflammatory effect in the lungs which can result in significant steroid sparing activity[16].

CONCLUSION

Theophylline and doxofylline consistently improved FEV1, FVC, and the FEV1/FVC ratio over time in COPD patients. Doxofylline had a significantly greater, but not statistically significant, effect on FEV1 than did theophylline on FEV1/FVC. In addition, doxofylline showed a safer profile than theophylline. However, there was no statistically significant difference in the therapeutic effects observed. The differences between these drugs could be better understood by additional clinical and pharmacokinetic studies.

Recommendation:

More randomized, controlled, and powered trials, as well as the longer follow-up, are needed to better determine the true efficacy and long-term adverse effects of both drugs

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