Original Research Article

Comparison of COPD patients on single inhaler and two separate inhalers for triple therapy – A short duration prospective cohort study

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A B S T R A C T

Introduction: Triple therapy (Long Acting Muscarinic Antagonist (LAMA), Long Acting $\beta 2$ Agonist (LABA), Inhaled Corticosteroid (ICS)) for Chronic Obstructive Pulmonary Disease (COPD) is available as single or separate inhalers. There is a dearth of studies in real-world scenario comparing them.
Materials and Methods: We followed up 33 moderate to severe COPD patients each on single inhaler (Tiotropium-Formoterol-Ciclesonide) and two separate inhalers (Tiotropium; Formoterol-Budesonide) for triple therapy for a period of three months. We compared socio-demography, Test of Adherence to Inhalers (TAI) score, baseline and improvement in FEV1, FEV1/FEV, St George Respiratory Questionnaire score (SGRQ) and Euro Qol 5 Dimension Scale score (EQ-5D) by independent t-test or Mann Whitney U test. The change in each group was compared with their baseline by paired t-test or Wilcoxon Signed Rank test.
Results: The groups were comparable at the baseline with respect to age, gender, smoking, FEV1/FEV, SGRQ, EQ-5D; TAI but, separate inhaler group was worser than single inhaler group with respect to baseline FEV1 (Severe COPD - 61% *Vs.* 30%) and spacer use (70% *Vs.* 100%) (p<0.05). Each group improved significantly on FEV1, FEV1/FEV, SGRQ and EQ-5D (p<0.05). Improvement in the group on separate inhalers was significantly (p<0.05) higher compared to group on single inhaler for FEV1 (median 5% Vs. 1%), FEV1/FEV (median 0.04 *Vs.* 0.02), SGRQ (mean -50.1 *Vs.* -25.5) and EQ-5D (median -3 *Vs.* -1).
Conclusion: Triple therapy improves patients by single or separate inhalers. Patients on separate inhalers had more improvement than patients on single inhaler without considering the confounding factors.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third most common cause of death worldwide.[1] It is largely a treatable condition but, remains under treated.[2] In response to this context, World Health Organization (WHO) considers improving access to effective therapies as one of the aim to control COPD.[3] Glucocorticoids, beta agonists, muscarinic antagonists, methylxanthines and phosphodiesterase-4 inhibitors are the medications available for treating COPD.[4] Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy recommends use of triple inhaled therapy with inhaled corticosteroids (ICS) glucocorticoid, long acting beta agonist (LABA) and long acting muscarinic antagonist (LAMA) for those who are at increased risk for frequent or severe exacerbations.[4]

Compliance to inhaled therapy was seen to be low (36%) in a report.[5] Higher number of inhalers was reported to be a reason for non-compliance among COPD patients.[6] Fixed dose combinations (FDCs) are assumed to improve compliance and they are also cheaper.[7] However, FDCs discourage titration of individual ingredients and encourage polypharmacy.[7] Conventionally triple therapy was prescribed with two inhalers – (ICS + LABA) and

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LAMA; single inhaler with all the three is a relatively new product.[8] Single Inhaler Triple Therapy products were not available when GOLD management strategy was formulated hence does not have its particular mention however, a panel of experts concurred that single inhaler has potential to improve adherence and for better outcome.[8] Vanfleteren LEGW et al., reported that there was only one study so far which compared triple inhaled therapy through single inhaler with three individual inhalers which showed both were equally effective.[9] In this context, we aimed to study the characteristics of patients on triple therapy with single inhaler and two separate inhalers and compare their outcome.

2. Materials and Methods

This was a prospective cohort study post obtaining an ethical committee clearance and consent from study subjects was conducted in the out-patient setting of department of pulmonary medicine in a teaching hospital in Kerala, the southern-most state of India. Patients with moderate to severe COPD (FEV1 30% – 79%) were enrolled into the study at the time of initiation on triple therapy.

We reviewed records of 15 patients each on single inhaler and two inhalers as pilot study. Standard deviation for improvement in FEV1 over a period of 3 months was 5.5 and difference in mean improvement of FEV1 was 3.8. The sample size was calculated as 33 in each group considering these values for an α error of 5% and power of 80%. Participants on single metered dose inhaler (MDI) and two metered dose inhalers were enrolled by consecutive sampling and were followed up for a period of three months. The study was completed over a period of six months from January to June, 2019.

Before and after the study period, the patients were evaluated for improvement in the pulmonary function which was evaluated by observing the changes in the FEV1 and FEV1/FVC values in pulmonary function test (PFT), improvement in the symptoms by using St. George's Respiratory Questionnaire (SGRQ) and quality of life by Euro Qol 5 Dimension scale (EQ-5D). Test of Adherence to Inhalers (TAI) Questionnaire was applied at the end of three months. SGRQ has three constructs – symptoms, activity and impact on social and physiological functioning. Worst possible status is represented by score of 100 and best possible health status score is represented by score 0.[10] TAI questionnaire has 12 items, first 10 items were rated on likert scale 1 to 5 and two questions have scores 1 and 2, and were to be answered by the health professional.[11] Higher scores represents better adherence. EQ-5D has dimensions of mobility, self-care, usual activities, pain/ discomfort and anxiety/depression.[12]

Age, FEV1, FEV1/FEV, SGRQ, TAI and EQ-5D were treated as continuous variables. Gender and smoking status were treated as categorical variables. Baseline characteristics and values of both groups were compared by independent t-test or Mann Whitney U test and chi square test or Fisher exact test appropriately. Change in FEV1, FEV1/FVC, SGRQ, EQ-5D before and after treatment in each group were analysed separately by paired t-test or/Wilcoxon signed rank test appropriately. The changes in groups were compared by independent t-test or Mann Whitney U test appropriately.

3. Result

There were 33 patients each on single inhaler triple therapy (Tiotrpium 9μg – formoterol 6μg – ciclesonide 200μg, 1 Puff BD) and two inhaler triple therapy (Tiotropium 9μg; Formoterol 6μg – budesonide 200μg, both 1 puff BD). Comparison of socio-demographic features of the groups is presented in Table 1.

Mean age of patients on single inhaler was 70.9 years (sd-7.8) and that of patients on two inhalers was 70.1 years (sd-8.3). In both groups, proportion of male patients was predominant. In the group on single inhalers, 29 (87.8%) were males and in the group on two inhalers, 26 (78.8%) were males. Self reported status of tobacco smoking was comparable in both groups. In both group about 1/10th were smoking currently and more than half were past smokers.

Table 2 compares other baseline characteristics of the participants. At the time of initiation on triple therapy, average FEV1 of the group on single inhaler was 54.9% (sd-11.7%) and that of the group on two inhalers was 46.9% (sd-12.8%). Significantly higher proportion of patients on separate inhalers (60.6%) had severe COPD than patients on single inhaler (30.3%). The groups were comparable with respect to FEV1/FEV. All the patients on single inhaler were using spacer and among those who were on two inhalers, 23 (69.7%) were using spacer. Median score of Test of Adherence to Inhalers (TAI) were not statistically significant between the groups. The groups were comparable with respect to quality of life at the time of enrollment with respect to scores on St. George's Respiratory Questionnaire (SGRQ) and Euro Qol 5 Dimension scale (EQ-5D).

Patients on triple therapy by single inhaler had a significant improvement after three months of treatment, compared to their baseline (Table 3). Median change in FEV1 was 1% and this improvement was statistically significant (p<0.001). There was significant improvement (median – 0.02) in FEV1/FEV. Quality of life (SGRQ and EQ-5D) improved significantly by mean score of 25.5 and median score of 1 respectively (p<0.001).

Patients on triple therapy by two inhalers had a significant improvement after three months of treatment, compared to their baseline (Table 4). Median change in FEV1 was 5% and this improvement was statistically significant (p<0.001). There was significant improvement (median – 0.04) in FEV1/FEV. Quality of life (SGRQ and

Table 1: Socio-demography ofpatients on triple therapy

Characteristics	Single Inhaler Frequency (%)	Two Inhalers Frequency (%)	p-value
Age#	70.9 (7.8)	70.1(8.3)	0.659
Gender			
Male	29 (87.8%)	26 (78.8%)	0.509
Female	4 (12.2%)	7 (21.2%)	
Smoking status			
Current smoker	4 (12.2%)	3 (9.1%)	
Past smoker	22 (66.7%)	17 (51.5%)	0.289
Non-smoker	7 (21.2%)	13 (39.4%)	

\# Mean (SD), compared by independent t-test, †Chi square test with Yate's continuity correction, ‡Fisher's exact test

Table 2: Baselinecharacteristics of patients on triple therapy

Characteristics	Single Inhaler Frequency (%)	Two Inhalers Frequency (%)	p-value
Spirometry			
Grading by FEV1 (%)			
Grade C (Severe)	10 (30.3%)	20 (60.6%)	0.013
Grade B (Moderate)	23 (69.7%)	13 (39.4%)	
FEV1/FEV#	0.53 (0.07)	0.55 (0.10)	0.380
Characteristics of inhaler use			
Use of Spacer	33 (100%)	23 (69.7%)	<0.001
TAI score$	47 (43-48)	45 (43-46)	0.073
Quality of life			
SGRQ score#	151.4 (16.8)	154.0 (21.9)	0.587
EQ-5D score$	10 (9-11)	10(10-12)	0.340

\# Mean (SD), compared by independent t-test, †Chi square test, ‡Fisher's exact test, $ Median (Inter Quartile Range), compared by Mann Whitney U test, TAI - Test of Adherence to Inhalers, SGRQ - St. George's Respiratory Questionnaire, EQ-5D - Euro Qol 5 Dimension scale

Table 3: Outcome of patients on Triple Therapy by Single inhaler

Measure	At enrolment Median (IQR)	After three months Median (IQR)	Difference Median (IQR)	p-value
FEV1(%)	60 (47 – 64)	61 (50-66)	1 (1-2)	<0.001
FEV1/FEV	0.54 (0.51-0.59)	0.56 (0.52-0.60)	0.02 (0.01-0.02)	<0.001
SGRQ	151.4 (16.8)	125.9 (15.6)	-25.5 (14.2)	<0.001
EQ-5D	10 (9-11)	9 (8-10)	-1 (-2 – -1)	<0.001

†compared by Wilcoxon signed rank test, ‡mean, standard deviation; Compared by paired t-test, SGRQ - St. George's Respiratory Questionnaire, EQ-5D - Euro Qol 5 Dimension scale

Table 4: Outcome ofpatients on triple therapy by two inhalers

Measure	At enrolment Median (IQR)	After three months Median (IQR)	Difference Median (IQR)	p-value
FEV1(%)	45 (36 – 57)	53 (41 – 61)	5 (4 – 7)	<0.001
FEV1/FEV	0.53 (0.51 – 0.59)	0.58 (0.55 – 0.68)	0.04 (0.03 – 0.07)	<0.001
SGRQ	154.0 (21.9)	103.9 (18.6)	-50.1 (18.7)	<0.001
EQ-5D	10 (10 – 12)	8 (7 – 9)	-3 (-3 – -2)	<0.001

†compared by Wilcoxon signed rank test, ‡mean, standard deviation; Compared by paired t-test, SGRQ - St. George's Respiratory Questionnaire, EQ-5D - Euro Qol 5 Dimension scale

Table 5: Comparison of improvement in patients on single inhaler and two inhalersfor triple therapy

Change in Measure of	Single Inhaler Median (IQR)	Two Inhalers Median (IQR)	p-value
FEV1(%)	1.0 (1.0-2.0)	5 (4 – 7)	<0.001
FEV1/FEV	0.02 (0.01-0.02)	0.04 (0.03 – 0.07)	<0.001
SGRQ	-25.5 (14.2)	-50.1 (18.7)	<0.001
EQ-5D	-1(-2 – -1)	-3 (-3 – -2)	<0.001

†compared by Mann Whitney U test, ‡mean, standard deviation; Compared by independent t-test, SGRQ - St. George's Respiratory Questionnaire, EQ-5D - Euro Qol 5 Dimension scale

EQ-5D) improved significantly by mean scores of 50.1 and median score of 3 respectively (p<0.001).

The improvement in patients on triple therapy by two inhalers and single inhaler was compared (Table 5). It was seen that patients on two inhalers had significantly better improvement compared to patients on single inhaler in FEV1 (median 5% Vs. 1% respectively), FEV1/FEV (median 0.04 Vs. 0.02 respectively), SGRQ (mean 50.1 Vs. 25.5), and EQ-5D (median 3 Vs. 1 respectively).

4. Discussion

This was a cohort study with three months follow up of two groups of 33 patients each on triple therapy for COPD by single inhaler and two inhalers. The group on single inhaler was significantly better with respect to FEV1 at baseline and higher proportion of patients were using spacer. There was a significant improvement in both groups in FEV1, FEV1/FEV, SGRQ and EQ-5D after three months of therapy compared to the baseline. The improvement in group on two inhalers was significantly higher than that of the group on single inhaler.

Triple inhaler therapy with ICS, LABA and LAMA is better than single or dual inhaled therapy in preventing COPD exacerbations.[13] Patients on single inhaler tend to have better adherence compared patients on multiple inhalers.[14] Hence it is logical to speculate that single inhaler as better than multiple inhalers to deliver triple therapy. A study done in United States among insured patients on multiple inhaler triple therapy suggested that single inhaler would improve adherence.[15] Triple therapy by single and separate inhalers was found to be equally effective in a randomized controlled trial.[16] However, there are not many studies comparing delivery of triple therapy by single or separate inhalers especially in real-world scenario.

In our study, the patients who were prescribed two inhalers improved better than patients on single inhaler. The potential confounders to be discussed in this context are - severity of the disease, difference in inhaled steroid (budesonide Vs. ciclesonide in two inhalers and single inhaler groups respectively) and use of spacer (70% Vs. 100% in two inhalers and single inhaler groups respectively).

In a study among patients with mild to moderate asthma, ciclesonide 320μg once daily was found to be more efficacious than 200μg twice daily.[17] In our study, patients on single inhalers used ciclosonide 200μg twice daily (400μg per day) and patients on two inhalers used budesonide 200μg twice daily. Significantly higher proportion of patients on two inhalers had severe disease compared to patients on single inhaler. Treatment outcome would be poorer if the grade of COPD is poorer.[18] Inhaled steroid and baseline FEV1% favoured a better outcome in the group of patients on single inhaler. All the patients on single inhaler used spacer whereas only 70% of the patients on two inhalers used spacer. Spacers are prescribed when the patients have poor coordination of firing MDI and inhaling aerosol.[19] Patients can use metered dose inhalers more effectively with spacer. However, it is difficult to ascertain how the spacers had contributed as techniques of inhalation were not assessed in this study.

Lack of data on many factors that contribute to treatment outcome is a major limitation of this study. We did not collect data on co-morbidities and co-medications. We had not assessed the inhalation techniques of individual patients. We have data on doses prescribed but, we lack data on actual number of doses patients used. The group on two inhalers have higher proportion of patients with severe COPD. It is plausible that patients with severe disease may use more doses to control their symptoms and this would explain better outcome in this group.

Triple therapy for COPD significantly improves patients with moderate or severe COPD by single or separate inhalers. Improvement of patients on separate inhalers was higher than the patients on single inhaler without considering confounding effects.

5. Source of Funding

6. Conflict of Interest

Nil.

7. Acknowledgement

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