ORIGINAL ARTICLE

Effectiveness of Triple Drug Fixed Dose Combination Inhaled Therapy in Severe COPD Patients

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ABSTRACT

Rationale: According to GOLD 2018 guidelines, inhaled corticosteroids are recommended along with long acting muscarinic antagonist (LAMA) and long acting beta-2 agonist (LABA) inhaler medications in Group D COPD patients who show frequent exacerbations and symptom severity. Therefore, the use of triple drug inhaled medication in such severe COPD patients become necessary.

Objectives: To know the effectiveness of inhaled triple drug medication in relation to spirometry, exercise tolerance, symptom control and prevention of exacerbations in severe COPD patients.

Method: 25 severe COPD patients were included in this hospital based study. Before initiating the triple drug inhaled medication the baseline parameters such as spirometry (FEV1), exercise tolerance (6 minute walking distance) and symptom control(CAT score, MMRC dyspnoea grading) are measured. 2 monthly follow-up till 6months of the study period is done. At each visit all the baseline parameters are reassessed.

Result: There is statistically significant (p=<0.01) improvement in the FEV1, CAT scoring, MMRC grading, 6 Minute Walking Distance in the 25 subjects following initiation of treatment with the triple drug inhaler medication over 6months observation period.

Conclusion: Triple drug inhaler medication in severe COPD patients is effective in improving airflow obstruction, symptom control, exercise tolerance and prevention of exacerbations.

Keywords: COPD, triple drug, MMRC, CAT Scoring

INTRODUCTION

GOLD 2018 defines chronic obstructive pulmonary disease (COPD) as a chronic, progressive and treatable disease characterized by persistent airflow limitation caused by damage to alveolar and or airway wall due to inhalation of environmental toxic noxious gas or particle.[1] Exacerbations and comorbities contribute to the overall severity of patients. [2,3] The destruction of lung parenchyma, increased by subtended inflammatory processes, leads to loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes the ability of the airways to remain opened during expiration.[3,4]

COPD management is a major healthcare problem, and numerous recommendations/guidelines were created to increase appropriateness hence to address the unmet need of patients remaining symptomatic, so to improve patients benefit and reduce exacerbation risk, [5] International guidelines such as the GOLD (Global Strategy for Diagnosis, Management and Prevention of COPD) provide guidance to physicians in treating COPD. [4]

COPD patients usually show neutrophilic inflammatory response to the environmental toxic gas or particle. However it is found that those patients who show atopy or has family history of atopy, asthma will show eosinophilic inflammatory response also.[6] Therefore the idea of adding an inhaled corticosteroid as a medication in these patients comes into picture.

Till date, long acting muscarinic antagonist (LAMA) or LAMA and long acting beta 2 agonist (LABA) has served as a better treatment option in COPD patients [3]. The use of inhaled corticosteroids in addition to LABA and LAMA is seen to be effective in following patients:

- Allergy to dust, smoke and seasonal variation.
- Frequent episodes of exacerbations requiring emergency room visits.
- Spirometry showing post bronchodilator FEV1 reversibility but <12% or <200ml [7].
- Family history of atopy, bronchial asthma.

Triple drug inhaled therapy delivered in a single inhaler dose reduces moderate to severe exacerbations

in COPD to a greater extent than dual inhaler therapy in patients at high risk for exacerbations, according to several studies such as IMPACT trial[8] and TRINITY trial[9].

METHODOLOGY

This is a hospital based study conducted from July 2017 to June 2018 in 25 severe COPD patients. These subjects were either not taking any inhaler therapy or were on dual drug inhaler medication. All the patients were male ex-smokers. Those already on dual inhaler medication were stopped from taking it and after washout period of those medications were put on single dose inhaler containing triple drug medication (LAMA+LABA+ICS). Those who were not taking any medications were directly initiated with the triple drug inhaled medication. Prior to this, baseline parameters like Spirometry, MMRC grading, CAT score, 6 Minute Walking Distance and BODE Index were assessed in all the subjects.

Patients were asked to come to the OPD every 2months for a total duration of 6months. During these 6months, patients were asked to report any time if they feel worsening of their symptoms and those episodes were considered as exacerbations. Patients' frequencies of emergency room visits were noted. At each 2monthly visit, all the aforementioned baseline parameters were reassessed. At the end of 6months, the effectiveness of triple inhaler therapy was calculated by comparing the baseline values with the end of 6month values.

Inclusion criteria: Above 40 years male or female patients with smoking history >10pack years and stable severe COPD patients since past one month were included in the study

Exclusion criteria: Pregnant women or lactating mother; cases with history of allergy or hypersensitivity; who are not giving consent; cases requiring oral or parenteral steroids; who were vaccinated in a last year; who are on roflumilast as add on therapy; or cases having associated other severe co-morbid conditions were excluded from the study..

RESULTS

Minimum age in this study is 41yrs and maximum age is 74yrs. There are 11(44%) patients in age group 61-65 yrs followed by 7(28%) patients in age group 66-70yrs. There are 2(8%) patients each in the age group 41-45yrs, 51-55yrs and above 70 yrs. There is only 1 patient in the age group 56-60yrs (Table 1). All patients included in the study are male ex-smokers however depending on their smoking history in the past they are divided on the basis of their smoking index. There are 12(48%) patients having history of smoking index in the range 0-50 followed by 11(44%) patients with smoking index in the range 51-100. There are only 2(8%) patients with smoking index above 100 (Table 2). There is decrease in the frequency of emergency room visits by severe COPD patients after initiation of tripe drug inhaled medication as seen in table 3.

Table 1: Age wise distribution

Age group(years)	Patients (%)
41-45	2 (8)
46-50	0 (0)
51-55	2 (8)
56-60	1 (4)
61-65	11 (44)
66-70	7 (28)
>70	2 (8)
Total	25 (100)

Table 2: Smoking Index

Smoking Index	Patients (%)
0-50	12 (48)
51-100	11 (44)
101-150	2 (8)
Total	25 (100)

Table 3: Frequency of exacerbations

	Emergency Room visits (mean)
Before treatment	1.08
After treatment	0.8

Table 4: Baseline parameters

Parameters	Mean Values	
	Before treatmnt	After treatmnt
PFT	35%	44%
MMRC Grading	2.28	1.96
6 min walking distance	248.96m	270.88m
BODE Index	6.4	5
CAT Score	19.92	15.56

Table 5: Applying paired t test

	Mean	Standard Deviation	95%of CI	T	P value
PFT(0)-PFT(6)	-8.36	2.396	-9.35,-7.37	-17.45	<0.01
MMRC(0)-MMRC(6)	0.32	0.48	0.12,0.52	3.361	<0.01
6MWD(0)-6MWD(6)	-21.92	20.84	-30.52,-13.32	-5.258	<0.01
BODE(0)-BODE(6)	1.4	1.19	0.91,1.9	5.881	<0.01
CAT(0)-CAT(6)	4.36	2.94	3.15,5.57	7.409	<0.01

There is significant improvement in post bronchodilator FEV1, Modified Medical Research Council (MMRC) grading system of dyspnoea, 6minute walking test, BODE index score and COPD Assessment Test (CAT) score in our study as seen in the table 4 and 5.

The change in mean from before starting treatment and at the end of 6 month follow up in spirometry, MMRC scale of dyspnoea, 6 Minute walking test, BODE Index, CAT Score is -8.36, 0.32, -21.92m, 1.4 and 4.36 respectively. The change in standard deviation in PFT, MMRC Scale, 6MWD, BODE Index and CAT Score is 2.396, 0.48, 20.84, 1.19 and 2.94 respectively. The p value for all the parameters are <0.01 which is statistically significant.

DISCUSSION

The goals of COPD therapy are to prevent and control symptoms, reduce the frequency and severity of exacerbations and improve exercise tolerance[1]. Triple drug inhaled medication containing long acting muscarinic antagonist, long acting Beta- 2 agonist and inhaled corticosteroid has become an option for maintenance treatment of COPD and as a "step-up" therapy from single or double combination treatments[8].

In my study, the mean value for the frequency of emergency room visits before triple inhaled medication was 1.08 and after 6months of triple inhaled medication was 0.8 which shows improvement in the exacerbations in COPD patients and this is comparable to other studies as follows:

IMPACT trial [8] has shown that triple therapy with fluticasone furoate, umeclidinium and vilanterol resulted in a lower rate of moderate to severe COPD exacerbations (0.91per year) than fluticasone furoate-vilanterol or umeclidinium-vilanterol (1.07 per year). Rate ratio with triple therapy, 0.85; 95%CI, 0.8 to 0.9; 15% difference; p value <0.001.

TRINITY trial [9] has shown moderate to severe exacerbation rates with extrafine fixed triple therapy (0.46; 95% CI 0.41 to 0.51). Fixed triple inhaled therapy was superior to tiotropium alone (rate ratio 0.80; 95% CI 0.69 to 0.92; p value=0.0025).

FULFIL trial [10] also showed statistically significant reduction in exacerbations with triple therapy versus dual ICS/LABA therapy (35% reduction; 95% CI 14 to 51; p value = 0.002).

In Rojas-Reyes et al trial included total 4 studies showed reduction in all cause hospitalizations with the use of combined therapy with tiotropium and LABA/ICS (0.61; 95%CI 0.4 to 0.92; 2 studies; n=961) [11].

In Xie F et al review on Triple therapy for management of COPD which included 4 trials also concluded that hospitalization rates due to COPD exacerbations were significantly reduced with triple therapy compared to long acting muscarinic antagonist monotherapy (rate ratio 0.53; 95% CI 0.33 to 0.86 and 0.35; 95%CI 0.16 to 0.78) [12].

In my study, improvement in mean value of FEV1 was -8.36; 95% CI -9.35 to -7.37; p value <0.01 which is comparable to other studies given below. In TRINITY trial, for 52week pre-dose FEV1, fixed triple dose inhaler was superior to tiotropium (mean difference 0.061L[95%CI 0.037 to 0.086]; p value <0.0001) [9]. In FULFIL trial, mean changes from baseline in FEV1 at 24 week for triple therapy (n=911) was 142ml (95% CI 126 to 158) [10]. In Xie F et al review in Triple therapy for COPD improvement in lung function as measured by FEV1was (with mean value 0.05L, 95% CI 0.00 to 0.11; 3 trials) [12].

In our study we have used BODE Index as a measure of quality of life which showed mean value 1.4; 95% CI 0.91 to 1.9; p value <0.01. There was significant improvement in quality of life of COPD patients on triple inhaler medication which is also seen in the studies given below. In FULFIL trial, mean changes from baseline SGRQ (Saint George Respiratory Questionnaire) scores was -6.6 units(95% CI -7.4 to -5.7) [10]. In Rojas –Reyes et al study, SGRQ scores showed statistically significant improvement in total scores with use of tiotropium and ICS/LABA compared with tiotropium alone (mean difference -3.46; 95%CI -5.05 to -1.87; 4 studies, n=1446) [11]. In Xie F et al review on Triple therapy for COPD showed significant improvement in quality of life (with mean difference 3.75; 95% CI 1.56 to 5.94; 2 trials) [12].

CONCLUSION

Triple drug inhaled medication is effective in improving symptom control and frequency of exacerbations in severe COPD patients. This makes triple therapy an attractive combination in COPD.

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