

Comparative Analysis of Peak Inspiratory Flow Rate at Discharge and Three-month Follow-up in Severe Acute Exacerbation of COPD Patients using Metered Dose Inhalers versus Dry Powder Inhalers: A Prospective Observational Study

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ABSTRACT

Introduction: Patients discharged following hospitalisation for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) are prescribed Metered Dose Inhalers (MDI), Dry Powder Inhalers (DPI), or nebulisers. Drug dispersion from the inhaler and deposition in the lung depends on Peak Inspiratory Flow Rate (PIFR) among other factors. A low PIFR results in suboptimal drug delivery and is a risk factor for readmission.

Aim: To estimate PIFR at discharge following AECOPD, assess the type of inhalers prescribed at discharge, and estimate the mean change in PIFR at three months follow-up in patients using MDI and DPI.

Materials and Methods: A prospective observational study was conducted at a tertiary care hospital, Goa Medical College, Goa, India on 138 patients over 15 months from November 2018 to February 2020. A sample size of 138 was calculated, and the study duration was 15 months. Patients admitted with AECOPD were enrolled in the study after obtaining informed consent. At discharge, baseline characteristics and co-morbidities were recorded, and PIFR was measured using an in-check dial peak inspiratory flow meter without resistance. Inhalers prescribed by the treating physician were verified and checked for errors.

PIFR was measured at three months of follow-up. Optimal PIFR was defined as PIFR of ≥ 60 L/min. Statistical analysis was performed using the Statistical Package for Social Science Programs (SPSS) version 24.0 (IBM Corp, SPSS Inc, Chicago, IL). A paired t-test assessed the change in PIFR at discharge and three months follow-up, and Pearson's correlation test was used to assess the correlation between continuous variables.

Results: Total 138 were enrolled with a mean age of 69.8 ± 7.5 years, 87 (63%) were males. The mean PIFR at discharge was 58.9 ± 24.7 L/min. 85 (61.6%) had suboptimal PIFR and were older [71.9 ± 7.8 versus 66.3 ± 5.6 , p -value=0.01]. A total of 59 (69.4%) with suboptimal PIFR received MDI. At three months, the suboptimal PIFR group receiving MDI showed a mean change in PIFR of 18.6 ± 7.7 , p -value<0.001 while with DPI mean change was -3.8 ± 6.3 , p -value=0.005.

Conclusion: 61.6% had suboptimal PIFR at discharge following hospitalisation with AECOPD. Patients with suboptimal PIFR receiving MDI showed improvement in PIFR at three months, while those with suboptimal PIFR using DPI showed significant deterioration. Identifying patients with suboptimal PIFR will aid appropriate prescription of inhaler devices.

Keywords: Chronic obstructive pulmonary disease, Cognitive function, Drug delivery system, Nebulisers

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease 2023 report defines Chronic Obstructive Pulmonary Disease (COPD) as a heterogeneous lung condition characterised by chronic respiratory symptoms due to abnormalities of the airways and/or alveoli that cause persistent, often progressive airflow obstruction [1]. Currently ranked as the third most common cause of death globally, COPD is a significant source of both morbidity and mortality [2]. A 90% of these fatalities take place in nations with low and moderate incomes [3,4].

Patients with COPD are known to have repeated exacerbations leading to worsening of lung function and death. Adequate maintenance treatment with Long-acting Beta 2 Agonist (LABA) and Long-acting Muscarinic Antagonist (LAMA) with or without inhaled steroids is advocated for the prevention of COPD exacerbations, symptom control, and improvement of Quality Of Life (QOL) [5]. These medications are delivered by inhalers such as pressurised MDIs (pMDI), DPIs, Soft Mist Inhalers (SMI), or nebulisers. pMDIs require hand-breath synchronisation, which can be challenging for elderly patients and those with arthritis. This limitation is addressed by DPIs or by using spacers with pMDIs. Optimal drug delivery to the lungs through inhaler devices depends on adequate Peak

Inspiratory Flow Rate (PIFR), cognitive function, and manual dexterity [6,7]. In a DPI, the patient must inhale with sufficient flow to cause deaggregation and dispersion of the medication powder [8]. For a pMDI device, a slow inhalation after actuation ensures a flow of about 30 L/min, which is the recommended flow rate when using a pMDI [9].

The maximum flow produced during a forced inspiratory maneuver is known as the PIFR. It is normally measured without resistance. The PIFR has a good correlation with the acceleration of inhalation, which is responsible for drug delivery. When inhaling through the DPI device, the internal resistance of the device impacts the PIFR generated for drug dispersion [10]. Smaller particles produced by a high flow rate enable better lung deposition [11]. The turbulent energy required for deaggregation is a product of the inhaler's resistance and subsequent flow generated [12]; hence, a high-resistance device may require a low PIFR for de-aggregation. In-vitro testing of DPIs is conducted by pharmaceutical companies at a PIF of 60 L/min for two seconds to assess the dose emitted [13]. To actuate the DPI, a minimal flow of 30 L/min is required to de-aggregate the dose into fine particles of less than five microns. A minimum inspiratory flow of 30 L/min is necessary to obtain a

certain therapeutic effect; however, when PIF is >60 L/min, the total and fine particle doses released by a DPI are optimal [14]. It has been observed that drug deposition in the lung with DPIs can be as low as 15%, depending on the amount of inhalation flow [15]. Various DPIs have minimal and optimal PIFRs. The most common DPI device available at present tertiary care hospital is an Aeroliser with a minimal PIFR of 40 L/min and a maximum of 65 L/min.

The PIFR measured with a spirometer has no correlation with PIFR measured with inhaler-imposed resistances. The lack of consistent association between PIFR and spirometric parameters like Forced Expiratory Volume 1 (FEV1) and FEV1% predicted suggests that spirometry alone cannot be utilised to select an inhaler device [12]. Many studies have used the In-Check Dial Peak Inspiratory Flow Meter to measure PIFR with and without resistances [13,16]. PIFR is reproducible in stable COPD, and one study showed no difference in PIFR measured between visits 317±225 days later [17]. Age and female gender affect PIFR, while AECOPD reduces PIFR, especially during AECOPD episodes requiring hospitalisation [18]. During hospitalisation, patients are treated with nebulisation of bronchodilators. If, these patients with low PIFR are discharged on DPIs, they have a higher chance of readmission with AECOPD [13]. There are no studies on the PIFR at discharge following AECOPD in present population.

Thus, the present study aimed to estimate the PIFR at discharge from the hospital following AECOPD, assess the type of inhaler device prescribed at discharge by the treating physician, and estimate the mean change in PIFR at three months in patients receiving medication through DPIs and MDIs.

MATERIALS AND METHODS

A prospective observational study was conducted at the Chest Diseases Hospital, Goa Medical College, a tertiary care teaching hospital in Goa, India. The hospital is a free center for patients suffering from respiratory diseases. The study was conducted over 15 months from November 2018 to February 2020, and approval was obtained from the Institutional Ethics Committee (Letter No: GMC/IEC/Oct-18/56). The study was performed following the Declaration of Helsinki.

Inclusion and Exclusion criteria: Patients ≥40 years of age hospitalised for AECOPD were enrolled after providing informed consent. Patients with AECOPD having tuberculosis, pneumonia, and lung cancer were excluded from the study.

Sample size calculation: The sample size was calculated with a power of 80%, a two-sided level of significance α of 0.05, an effect size of 0.5, and a standard deviation of change as 2.0. After accounting for a 10% loss to follow-up, a sample size of 138 was calculated.

Study Procedure

According to the recommendations set forth by the Global Initiative for Chronic Obstructive Lung Diseases, a patient was diagnosed with COPD if, the ratio of forced expiratory flow in one second to Forced Vital Capacity (FVC) is less than 70% in a stable state [19], or if, they were diagnosed with COPD by a physician upon admission. Worsening of respiratory symptoms requiring systemic or oral corticosteroids, antibiotics, or both, was considered an acute exacerbation [20,21]. All patients were treated with standard therapy for AECOPD. The American Thoracic Society and the European Respiratory Society's guidelines for spirometry were followed [22]. Exposure to smoking risk factors was measured in pack-years, and exposure to smoke from biomass fuel was reported in hour-years. Pack-years were calculated as the number of cigarette packets smoked per day multiplied by the number of years of smoking [23], while the hour-year calculation is based on the patient's average daily cooking hours multiplied by the number of years they had been using biomass fuel [24]. The PIFR was measured using an in-check

dial inspiratory flow meter (Clement Clarke International Ltd.), which measures inspiratory flow between 30-370 L/min. The patient keeps the mouthpiece in the mouth and inhales from Functional Residual Capacity (FRC) as fast and hard as possible, which causes air to be drawn through the meter, and a cursor moves along the scale to indicate the speed of inhalation. The highest of the three values was recorded on the day of discharge. A PIFR of 60 L/min or more was deemed optimal [14,25,26], while PIFR <60 L/min was considered sub-optimal PIFR. Since FRC fluctuates less from baseline values than residual volume in patients with AECOPD, in present study, PIFR was measured from FRC [27]. Other parameters captured were the type of inhaler (MDI/DPI) prescribed by the treating physician at discharge and previous instructions received on the inhaler technique. The inhaler technique was checked and corrected if, any errors were detected. All patients were discharged on LABA, LAMA, and Inhaled Corticosteroid (ICS). Patients were called for follow-up at three months from discharge, and PIFR was measured. Self-reported adherence to the use of inhalers by patients during the follow-up period was accepted.

STATISTICAL ANALYSIS

The statistical analysis was conducted using SPSS Programs version 24.0 (IBM Corp, SPSS Inc, Chicago, IL). The normality of data was assessed using the Shapiro-Wilk test. Continuous variables were represented by the mean and standard deviation (SD), while categorical variables were represented by percentages. Differences between the two groups were examined using independent Student's t-test and Chi-square test. A paired t-test was used to assess the change in PIFR at three months of follow-up. Correlation analysis was performed using Pearson's correlation test. A statistically significant result was defined as a p-value <0.05.

RESULTS

A total of 138 patients were enrolled with a mean age of 69.8±(7.5) years. Eighty-seven (63%) were males, and ninety-seven (70.3%) were smokers. The mean PIFR at discharge was 58.9±(24.7). Eighty-five (61.6%) had sub-optimal PIFR, and fifty-three (38.4%) had optimal PIFR at discharge. The sub-optimal PIFR group was older with a mean age of 71.9±7.8 years compared to 66.3±5.6, p-value=0.01. Age had a negative correlation with PIFR at discharge, r=-0.417, p-value=0.001. Ischaemic heart disease, diabetes mellitus, and hypertension were significantly associated with sub-optimal PIFR. Twenty-six (30.6%) patients in the sub-optimal PIFR group with a mean PIFR of 44.6±(7.1) were prescribed DPIs at discharge. The baseline characteristics of the study population has been depicted in [Table/Fig-1].

Variable	Whole group (N=138)	Optimal PIFR (n=53)	Sub-optimal PIFR (n=85)	p-value
Age (years) (mean±SD)	69.8±7.5	66.3±5.6	71.9±7.8	0.01*
Males n (%)	87 (63)	37 (42.5)	50 (57.5)	0.19
Females n (%)	51 (36.9)	16 (31.4)	35 (68.6)	
Length of stay (mean±SD)	7.8±3.7	7.4±2.7	7.8±3.7	0.76
Smokers n (%)	97 (70.3)	35 (66)	62 (72.9)	0.07
Pack years (mean±SD)	45.8±13.5	44.1±11.9	46.8±14.3	0.27
Hour years (mean±SD)	157±31.6	141.1±34.8	169.5±22.7	0.53
DM n (%)	55 (39.9)	15 (28.3)	40 (47.1)	0.02*
HTN n (%)	86 (62.3)	25 (47.2)	61 (71.8)	0.004*
IHD n (%)	37 (26.8)	9 (9.4)	28 (32.9)	0.04*
DPI n (%)	67 (48.5)	41 (77.3)	26 (30.6)	0.005*
MDI n (%)	71 (51.4)	12 (22.6)	59 (69.4)	
Previous use of inhalers n (%)	83 (60.1)	39 (73.8)	44 (51.8)	0.01*

[Table/Fig-1]: Baseline characteristics of study population.

PIFR: Peak inspiratory flow rate; DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischaemic heart disease; DPI: Dry powder inhaler; *Statically Significant; Test of significance: Student's t-test; Chi-square test

The mean PIFR at discharge, which was 58.9 ± 24.7 , improved to 69.2 ± 25.4 at three months of follow-up; $p < 0.001$ has been represented in [Table/Fig-2]. The change in mean PIFR at three months of follow-up in the sub-optimal and optimal PIFR groups, which were 11.7 (9.0, 14.5), p -value=0.003 and 7.9 (5.4, 10.3), p -value=0.005, respectively has been shown in [Table/Fig-3].

Parameters	PIFR at discharge Mean \pm SD	PIFR at 3 months Mean \pm SD	p-value
Whole group	58.9 \pm 24.7	69.2 \pm 25.4	<0.001*
DPI	68.8 \pm 26.0	73.1 \pm 32.0	0.01*
MDI	49.7 \pm 19.6	65.6 \pm 16.4	<0.001*

[Table/Fig-2]: Mean PIFR at discharge and three months of follow-up.

*Statistically significant; DPI: Dry powder inhaler; MDI: Metered dose inhaler; Test of significance: Student's t-test

PIFR group	PIFR	PIFR Mean \pm SD	Mean change in PIFR (95%CI)	p-value
Suboptimal PIFR	Discharge	43.1 \pm 7.5	11.7 (9.0,14.5)	0.003*
	3 months FU	54.9 \pm 12.9		
Optimal PIFR	Discharge	84.3 \pm 21.4	7.9 (5.4,10.3)	0.005*
	3 months FU	92.2 \pm 23.5		

[Table/Fig-3]: Change in mean PIFR at 3-month follow-up in suboptimal and optimal PIFR group.

*Statistically significant; FU: Follow-up; Test of significance: Student's t-test

The mean change in PIFR in the sub-optimal and optimal PIFR groups at three months of follow-up based on the type of inhalers prescribed at discharge has been shown in [Table/Fig-4]. In the sub-optimal PIFR group, the use of MDI improved PIFR from $42.5 \pm (7.7)$ to $61.1 \pm (9.6)$, $p < 0.001$, while the use of DPI led to a deterioration of PIFR from $44.6 \pm (7.0)$ to $40.7 \pm (6.8)$, p -value=0.005. In the optimal PIFR group, the use of DPI showed an improvement from $84.1 \pm (21.5)$ to $93.6 \pm (23.5)$, $p < 0.001$, while there was no statistically significant change with MDI use.

PIFR group	Type of inhaler	PIFR	Mean (SD)	Mean change PIFR	95% confidence interval of difference		p-value
					Lower	Upper	
Suboptimal PIFR	DPI	Discharge	44.6 \pm 7.0	-3.8	-6.4	-1.2	0.005*
		Three-month	40.7 \pm 6.8				
	MDI	Discharge	42.5 \pm 7.7	18.6	16.6	20.6	
		Three-month	61.1 \pm 9.6				
Optimal PIFR	DPI	Discharge	84.1 \pm 21.5	9.5	6.9	12.0	<0.001*
		3 months	93.6 \pm 23.5				
	MDI	Discharge	85.0 \pm 21.9	2.5	-3.6	8.6	
		Three-month	87.5 \pm 24.1				

[Table/Fig-4]: The mean change in PIFR in sub-optimal and optimal PIFR group at 3-month follow-up as per use of inhalers at discharge.

*Statistically significant; Test of significance; Paired t-test

DISCUSSION

The study demonstrated that the mean Peak Inspiratory Flow Rate (PIFR) at discharge following Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) was $58.9 (24.7)$ L/min, with 61.6% of patients having a sub-optimal PIFR of < 60 L/min. The sub-optimal PIFR group had a mean PIFR of $43.1 (7.5)$ L/min, while the optimal PIFR group had $84.3 (21.4)$ L/min at discharge. Patients with sub-optimal PIFR were females, older age and had co-morbidities such as ischaemic heart disease, hypertension, and diabetes mellitus. Furthermore, in the sub-optimal PIFR group, the use of Metered Dose Inhaler (MDI) improved PIFR, while the use of Dry Powder Inhaler (DPI) led to a deterioration of PIFR.

There is recent interest in studying PIFR in patients with severe AECOPD. However, there are very few studies in the literature that assess the PIFR at discharge following AECOPD [13,18]. Also, there are no guidelines for the assessment of PIFR at discharge. The present study demonstrated that 61.6% of patients had sub-optimal PIFR at discharge. These patients were females, older, and had significant co-morbidities. In hospitalised patients with AECOPD, Loh CH et al., also evaluated PIFR without resistance and found that 52% of patients had suboptimal or poor PIFR at discharge [13]. Sharma G et al., measured PIFR against resistance for Diskus[®] DPI in hospitalised patients with AECOPD at discharge and reported that the mean PIFR was $71 (22.2)$ L/min, and 31.7% had a low PIFR of < 60 L/min [18]. In the current study, there were older patients with a mean age of $69.8 (7.5)$ compared to Loh CH et al., $64 (11.3)$, which probably contributed to a higher proportion of patients with sub-optimal PIFR, as higher age was associated with low PIFR. Similarly, Sharma G et al., also reported low PIFR in female and older patients [18].

Loh CH et al., reported co-morbidities in their study with a mean Charlson's comorbidity index of 5.4 [13]. The current study did not use Charlson's comorbidity index, but a significant number of patients in this study with sub-optimal PIFR had co-morbidities like ischaemic heart disease, hypertension, and diabetes mellitus.

At three months of follow-up on triple inhaler therapy, the mean PIFR improved from $58.9 (24.7)$ L/min to $69.2 (25.4)$ L/min. In the sub-optimal PIFR group, the PIFR of individuals receiving MDI improved significantly, while those receiving DPIs showed significant worsening. A PIFR of 30 L/min is the ideal flow for MDI; hence, an improvement in PIFR was observed in present group [28].

In the current study, 30.6% of patients with sub-optimal PIFR received medication through DPI, while in a study by Sharma G et al., 70.6% were discharged on a DPI device while having a low PIFR [18]. Borgström L et al., reported that when PIFR was reduced from 58 L/min to 36 L/min in 10 healthy participants, drug deposition using radiolabeled budesonide in a Turbuhaler device decreased from 28% to 15% [29], showing that adequate PIFR is essential for optimum drug delivery. There is no study in the literature that has assessed improvement in PIFR following discharge after hospitalisation for AECOPD. The present study demonstrated that when MDI was prescribed for patients with sub-optimal PIFR at discharge following AECOPD, it significantly improves PIFR. Those with sub-optimal PIFR receiving DPI showed a significant worsening of PIFR. Clark AR et al., stated that patients who are unable to reach a flow rate of 60 L/min cannot generate a pressure drop of < 0.5 kPa (5 cm of water) and hence should use inhaler devices such as MDI, SMI, or nebulisers [30]. Also, sub-optimal PIFR is a risk factor for exacerbations and readmissions as reported by Loh CH et al., [13]. In current practice, the choice of inhaler device is based on availability, affordability, and the ability to use it correctly. The present study highlighted the need to assess PIFR at discharge and to prescribe the type of inhaler device as per PIFR.

Limitation(s)

There are a few limitations to note in present study. The main outcome assessed was PIFR at discharge and mean change in PIFR at three months only. The study was not powered to assess improvement in PIFR in a subgroup of patients with suboptimal PIFR receiving MDI or DPI. In a previous study having small sample size, it was demonstrated that patients with suboptimal PIFR of < 60 L/min against Diskus (DPI) resistance receiving nebulised arformoterol had greater volume responses measured by FVC and IC at two hours compared to patients using a DPI [26]. Hence, a small sample size may not affect the outcome of present study. However, a larger sample size of patients with suboptimal PIFR would help in the generalisation of results. Another limitation of the current study was that self-reported adherence to medications was accepted.

CONCLUSION(S)

The study demonstrated that a high proportion of patients at discharge following AECOPD had suboptimal PIFR, and medications delivered to them through MDIs significantly help improve PIFR compared to DPIs. Because a COPD exacerbation might impair PIFR due to lung hyperinflation, it is critical to evaluate PIFR at discharge to establish whether the patient can adequately inhale dry powder from a DPI. Authors recommended that measurement of PIFR be incorporated into the discharge protocol of patients admitted with AECOPD and that the medication delivery device be appropriately prescribed. This is critically important in order to optimise the use of inhalers in a real-world setting.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Mar 26, 2024
- Manual Googling: May 20, 2024
- iThenticate Software: Jun 17, 2024 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 24, 2024**
Date of Peer Review: **May 17, 2024**
Date of Acceptance: **Jun 18, 2024**
Date of Publishing: **Aug 01, 2024**