PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial
AUTHORS	Hua, Jianlan; Zhang, wei; Cao, Hui-fang; Du, Chun-ling; Ma, Jia-yun; Zuo, Yi-hui; Zhang, Jing

VERSION 1 - REVIEW

REVIEWER	P.N.R. Dekhuijzen Radboud umc, Nijmegen, the Netherlands
REVIEW RETURNED	05-Nov-2019

GENERAL COMMENTS	An important issue in the clinic, appropriate study design and primary and secundary endpoints. Questions and suggestions: 1. Perhaps good to emphasize that measures of expiratory flo limitation (e.g. FEV1) do not predict inspiratory flow parameters. 2. Consider subgroup analysis on factors which may influence outcome. 3. When mentioning PIFR of e.g. 60 L/min: please indicate if this is through a resistance. 4. page 8 line 17: please motivate why these two preparations is being used. 5. page 12 line 6: this is a rather subjective list of items. The items have a very different weight regarding the criterium 'unsatisfactory'. 6. page 5 line 39: suboptimal in stead of poor.

REVIEWER	Andrea Melani Pneumologia, Siena Azienda Ospedaliera Universitaria Senese, Siena, Italy
REVIEW RETURNED	18-Nov-2019

GENERAL COMMENTS	Several studies have found that a reduced peak inspiratory flow (ie,

	below the minimum necessary for effective use of a DPI) is common in subjects with COPD exacerbations requiring hospitalization. Loh et al reported that subjects with impaired peak inspiratory flow were at a greater risk of all-cause 90-day re-hospitalization, whereas this was not found in the study by Sharma. Broeders et al and Bruscoli et al. have observed that peak inspiratory flow changes from exacerbation to stable state. This randomized controlled protocol study aims to evaluate PIF rates in COPD subjects recovering from an acute exacerbation and to associate this value to outcome. The idea is very good. The primary outcome is 30-day treatment failure rate I understand that all eligible subjects were consecutively enrolled. May you confirm or definite this point into the text. Why did authors insert the cut-off of 80 years? I suggest to enlarge this threshold as many subjects are old and low PIFR rates are common in the elderly. Why did authors insert a 5-7 day hospitalization as an inclusion criterium. I suggest to take off even this limit. PIFR<20lpm is another exclusion parameter. Why? How and when do you measure PIFR? At entry? During hospitalization? At discharge? How many attempts of InCheck Dial measurements did you perform? Did you select the mean or the highest value? Which is the preset resistance that you put into the Incheck Dial? Please add the detail of pre-hospitalization inhaled treatment. I see that you regularly prescribe a LABA/ICS at discharge. Please discuss in a better way the phrase “for symptomatic subjects before hospitalization Spiriva was also prescribed”? Which does mean? How did you Respimat or Handihaler? I do not understand your choice to be prescribed a DPI (Symbicort?) if PIFR is higher than 60 lpm, whereas a pMDI with an add-on spacerfor lowr PIPFRs? On the contrary, you write that, the control group will receive either the DPI or the MDI and and-on spacer in accordance to the physician judgment. ??? As authors know the minimally effective PIFR depends on the DPI. The cut-off is 20 lpm for HandiHaler, 30 for Disksu and Turbohaler. Moreover, the optimal PIF rate is 30 lpm for Diskus and 60 lpm for Turbohaler Please review the checklist that you will use to describe inhaler technique? For instance, position is important during preparation for Symbicort.ì, but did not report this step. Which is the questionnaire that did use for satisfaction with inhaler device? I do not understand the role of Diskus. When did you prescribe Diskus? Why did you not control inhaler technique with Spiriva respimat and handihaler. Importantly authors should focus their research either on the value of inhaler education or (better, in my opinion) on the prognostic value of PEFR at discharge of AECOPD

REVIEWER	FEDERICO LAVORINI University of Florence, Italy
REVIEW RETURNED	20-Nov-2019

GENERAL COMMENTS	The aim of this sudy project to investigate whether choice of inhaled device based on peak inspiratory flow (PIF) value may reduce COPD readmission to hospital after discharge from an exacerbation. The idea is of interest; however, I have some concerns about the methodology proposed by the Authors. A clear hypothesis is also lacked. The Authors provide few details on the matching criteria between the PIF group and controls, particularly on discharge criteria (too subjective with no data) as well as on the treatment (drugs and dosage) prescribed at the discharge. Ideally, the same drug and dosage should be prescribe (either via a pMDI or DPIs) to patients. In addition,the list of errors needs to be carefully review: why preparation errors wih the Diskus (i.e. do not move the lever) is not included in the list of errors ? I also recommed the Authors to provide more details about the modalities to assess inhalation technique and about the training of the patients. Patients' satisfaction should be objectively evaluated by means of validated questionnaires.

VERSION 1 – AUTHOR RESPONSE

Reply to P.N.R. Dekhuijzen (reviewer 1):

Thank you for all your valuable suggestions first. We have modified the manuscript based on your suggestions. We will reply to you point by point as follow.

Major concerns 1:

Perhaps good to emphasize that measures of expiratory flo limitation (e.g. FEV1) do not predict inspiratory flow parameters.

Reply 1:

Thank you for this valuable suggestion! We have added remarks on this issue in Introduction: Moreover, it should be noted that expiratory flow rate (such as FEV1) is not correlated linearly with inspiratory flow parameters, and it do not predict PIFR.

Major concerns 2:

Consider subgroup analysis on factors which may influence outcome.

Reply 2:

Thank you for your suggestion! We will accordingly perform subgroup analysis by exacerbation history and GOLD grades. We reflect this part of the modification in the Method: Subgroup analysis by exacerbation history and GOLD grades will be performed to rule out the influence of confounding factors to the certain extent.

Major concerns 3:

When mentioning PIFR of e.g. 60 L/min: please indicate if this is through a resistance.

Reply 3:

When we mention PIFR, the resistance of the InCheck DIAL® is set as zero. And we have modified and emphasized it in the Introduce and Study outline of Method.

Major concerns 4:

page 8 line 17: please motivate why these two preparations is being used.

Reply 4:

We use these two preparations to study whether training patients to use inhalers can reduce the error rate of inhaler and the rate of treatment failure. It has been mentioned in the Introduction and Discussion.

Major concerns 5:

page 12 line 6: this is a rather subjective list of items. The items have a very different weight regarding the criterium 'unsatisfactory'.

Reply 5:

We planned to use satisfaction with inhalers to evaluate patients' compliance. Satisfaction with inhaler use is not our primary endpoint due to the subjectivity of the evaluation. According to your suggestion, we will use FSI-10 questionnaire instead to evaluate patient satisfaction so as to improve its objectivity. We have modified it in the Endpoint of Method and FSI-10 questionnaire have been submitted in the supplementary file. The FSI-10 questionnaire is completed by patients themselves, which has been widely applied to assess patients' opinions about ease of use, portability, and usability of inhalers (ref 20 Perpina Tordera M, Viejo JL, Sanchis J, et al. [Assessment of patient satisfaction and preferences with inhalers in asthma with the FSI-10 Questionnaire]. Archivos de bronconeumologia 2008;44(7):346-52).

Major concerns 6:

page 5 line 39: suboptimal instead of poor.

Reply 6:

We have modified “poor” to “suboptimal” based on your suggestion.

Reply to Andrea Melani (reviewer 2):

Thank you for all your valuable suggestions first. We have modified the manuscript based on your suggestions. We will reply to you point by point as follow.

Major concerns 1:

Why did authors insert the cut-off of 80 years? I suggest to enlarge this threshold as many subjects are old and low PIFR rates are common in the elderly.

Reply 1:

We set the upper limit of age to 80 because committee ethics of our hospital does not approve the recruitment of patients over 80 years old.

Major concerns 2:

Why did authors insert a 5-7 day hospitalization as an inclusion criterium. I suggest to take off even this limit.

Reply 2:

We consider the remission after 5-7 days of standard treatment as the inclusion criterion because if patients take longer to relieve, they are more likely to have severe comorbidities, which leads to uncontrolled confounding factors between the two groups.

To increase comparability and reduce bias between the two groups, we employed remission after 5-7 days as an inclusion criterion.

Major concerns 3:

PIFR<20lpm is another exclusion parameter. Why?

Reply 3:

If PIFR is less than 20L/min, the patient's lung function is quite weak and is more likely to need aerosolized inhalation. Therefore, we excluded patients with a PIFR of less than 20 L/min.

Major concerns 4:

How and when do you measure PIFR? At entry? During hospitalization? At discharge? How many attempts of InCheck Dial measurements did you perform? Did you select the mean or the highest value? Which is the preset resistance that you put into the Incheck Dial?

Reply 4:

We will measure PIFR for patients who are randomized into the intervention group when they satisfy the inclusion/ exclusion criteria after 5-7 days of the treatment for AECOPD (V1). As shown in the flow chart of the study (Figure 1 has been modified to make it easy to understand), all hospitalized patients with diagnosis of AECOPD will be followed to check whether they meet inclusion criteria, i.e. (1) 40–80 years old; (2) patients with AECOPD whose acute respiratory symptoms have been controlled and met discharge criteria after 5-7 day-standard AECOPD treatment including atomized or inhaled bronchodilator plus oral or intravenous glucocorticoid (prednisone equivalent dose 40-50mg) or Pulmicort 2mg atomization twice daily plus broad-spectrum antibiotics; (3) patients with moderate and above COPD with a recorded spirometry measured in the stable disease status, ie, post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and

FEV1% predicted value <80%; (4) patients have signed an informed consent form. If yes, they will be enrolled and randomized into intervention or control group. For the intervention group, PIFR will then be tested.

Before measuring PIFR, we will first train patients to use the InCheck DIAL® correctly. After patients are able to reach their maximum of PIFR steadily, we will measure the PIFR 3 times and take the average as a result. We set the resistance of the InCheck DIAL® to zero when measuring PIFR. We have added this section to the Study outline of Method.

Major concerns 5:

Please add the detail of pre-hospitalization inhaled treatment.

Reply 5:

We will collect clinical characteristics including inhaled treatment before hospitalization of patients at V0 (Hospitalization±1 day). We have mentioned it at the Study step of Method.

Major concerns 6:

I see that you regularly prescribe a LABA/ICS at discharge. Please discuss in a better way the phrase “for symptomatic subjects before hospitalization Spiriva was also prescribed”? Which does mean? How did you Respimat or Handihaler?

Reply 6:

Symptomatic subjects means subjects with mMRC ≥ 2 and CAT≥ 10 before acute exacerbation. We have added instructions in the Study outline of Method. For these patients, open combination of LAMA/LABA/ICS will be given. Therefore, in addition to ICS/LABA, we prescribe Spiriva as a supplement for these patients, and choose handihaler or respimat according to PIFR. We have clarified this issue in the Methods.

Major concerns 7:

I do not understand your choice to be prescribed a DPI (Symbicort?) if PIFR is higher than 60 lpm, whereas a pMDI with an add-on spacerfor lowr PIPFRs? On the contrary, you write that, the control group will receive either the DPI or the MDI and and-on spacer in accordance to the physician judgment. ???As authors know the minimally effective PIFR depends on the DPI. The cut-off is 20 lpm for HandiHaler, 30 for Disksu and Turbohaler. Moreover, the optimal PIF rate is 30 lpm for Diskus and 60 lpm for Turbohaler.

Reply 7:

We agree with your comments. In order to study the effect of optimized inhalation therapy based PIFR measurements on improving the prognosis of AE patients, patients of PIFR group (the intervention group) will be given DPI (turbuhaler with or without handihaler) if PIFR is over 60 L/min, while they will be given pMDI if PIFR is less than 60 L/min. In our study, we choose to use Symbicort because it is the most widely available ICS/LABA in China, and therefore the cutoff of PIFR is set to 60L/min. For

the control group, the inhalers are to be chosen based on the current routine practice, i.e. according to physician judgement.

Major concerns 8:

Please review the checklist that you will use to describe inhaler technique?

For instance, position is important during preparation for Symbicort.ì, but did not report this step. Which is the questionnaire that did use for satisfaction with inhaler device?

Reply 8:

We have reviewed the checklist of device error and modified some of the items such as “Device is not held upright.” in Table 2 (The error rate of inhalation device use) based on your suggestions.

Major concerns 9:

I do not understand the role of Diskus. When did you prescribe Diskus? Why did you not control inhaler technique with Spiriva respimat and handihaler.

Reply 9:

We do not allow to use Diskus in this study. When we prescribe DPI for patients, we use Symbicort turbuhaler® and Spiriva handihaler®. We have added the error of handihaler and respimat in the Table 2. (The error rate of inhalation device use). We will train patients to avoid mistakes and evaluate the rate of patient's inhaler error shown in Table 2.

It has been modified in the Method: Moreover, the InCheck DIAL® is an inhalation airflow training meter that can help educate and assess patients who use inhaler devices. When training the patient, we will set the corresponding resistance for the InCheck DIAL® according to the inhaler that the patient is prescribed. We will also explain to the patient the proper operation of the inhaler and demonstrate some common mistakes.

Major concerns 10:

Importantly authors should focus their research either on the value of inhaler education or (better, in my opinion) on the prognostic value of PEFR at discharge of AECOPD.

Reply 10:

This study focused on the effects of optimized inhalation therapy and inhaler education on reducing treatment failure. PIFR is measured to help select optimal inhalers. Our main research object is PIFR in the current study. We measure expiratory parameters such as FEV1 in order to evaluate the severity of airflow limitation, and subgroup analysis by exacerbation history and GOLD grades will be performed. We have added remarks on this issue in Introduction: Moreover, it should be noted that expiratory flow rate (such as FEV1) is not correlated linearly with inspiratory flow parameters, and it do not predict PIFR.

Reply to FEDERICO LAVORINI (reviewer 3):

Thank you for all your valuable suggestions first. We have modified the manuscript based on your suggestions. We will reply to you point by point as follow.

Major concerns 1:

The Authors provide few details on the matching criteria between the PIF group and controls, particularly on discharge criteria (too subjective with no data) as well as on the treatment (drugs and dosage) prescribed at the discharge. Ideally, the same drug and dosage should be prescribe (either via a pMDI or DPIs) to patients.

Reply 1:

Discharge criteria is defined by Expert Consensus on Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the People's republic of China,. It has been widely recognized in China and used to guide the diagnosis and treatment of AECOPD.

Considering the availability and price of medicines and the coverage of health insurance, we use Symbicort turbuhaler® and Spiriva handihaler® when we prescribe DPI for patients while Beclometasone/ Formoterol Foster® and Spiriva respimat® when we prescribe pMDI for patients. The dosage is determined by the requirements of the drug and the actual situation of the patient, which will be recorded and analyzed. Restricted by actual conditions, the drugs and dosages of the PIFR group and the control group are not exactly the same, which may affect our results, and we have considered it as the limitation of this study.

Major concerns 2:

In addition, the list of errors needs to be carefully review: why preparation errors wih the Diskus (i.e. do not move the lever) is not included in the list of errors ?

Reply 2:

We have reviewed the checklist of device error and modified some of the items such as "Device is not held upright." in Table 2 (The error rate of inhalation device use) based on your suggestions. In our study, we choose to use Symbicort because it is the most widely available ICS/LABA in China, and therefore the Diskus is not listed.

Major concerns 3:

I also recommend the Authors to provide more details about the modalities to assess inhalation technique and about the training of the patients.

Reply 3:

According to your suggestion, we have provided more details about assess and training of the patients in the Study outline of Method. When training the patient, we will set the corresponding resistance for the InCheck DIAL® according to the inhaler that the patient is prescribed. We will also explain to the patient the proper operation of the inhaler and educate to avoid common mistakes.

Major concerns 4:

Patients' satisfaction should be objectively evaluated by means of validated questionnaires.

Reply 4:

According to your suggestion, we will use FSI-10 questionnaire to evaluate patient satisfaction so as to improve its objectivity. We have modified it in the Endpoint of Method and FSI-10 questionnaire have been submitted in the supplementary file. The FSI-10 questionnaire is completed by patients themselves, which has been widely applied to assess patients' opinions about ease of use, portability, and usability of inhalers (ref 20 Perpina Tordera M, Viejo JL, Sanchis J, et al. [Assessment of patient satisfaction and preferences with inhalers in asthma with the FSI-10 Questionnaire]. Archivos de bronconeumologia 2008;44(7):346-52).

VERSION 2 – REVIEW

REVIEWER	Andrea Melani pneumologia/UTIP, Dipartimento vasi, cuore torace, Azienda Ospedaliera Universitaria Senese, Siena, Italy
REVIEW RETURNED	02-Jan-2020

GENERAL COMMENTS	Authors have improved the paper. I suggest that to change the following phrase (lines 42-52) that it not proper "Specifically, the results showed that both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than 60 liters/min (measured at 0 no resistance)11, which may result in ineffective inhalation of medications using a DPI". I suggest to write "Specifically, the results showed that using a DPI both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than a certain threashold 11" I also suggest that authors include the measurement of PIF rate even at hospital entry and not only at discharge during the hospitalization and they also measure the PIF rate at 60 lpm of resistance and only at 0 resistance. This can add some other information with scarce adjunctive work. At last I suggest to remove the sentence "shake the device" as error for the Foster MDI as it is a solution and it does not require shaking

REVIEWER	FEDERICO LAVORINI University of Florence
REVIEW RETURNED	24-Dec-2019

GENERAL COMMENTS	The authors have satisfactorily replied to the issues. I have no further comments.

VERSION 2 – AUTHOR RESPONSE

Reply to Andrea Melani (reviewer 2):

Thank you for all your valuable suggestions first. We have modified the manuscript based on your suggestions. We will reply to you point by point as follow.

Major concerns 1:

Authors have improved the paper. I suggest that to change the following phrase (lines 42-52) that it not proper "Specifically, the results showed that both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than 60 liters/min (measured at 0 no resistance) 11, which may result in ineffective inhalation of medications using a DPI". I suggest to write "Specifically, the results showed that using a DPI both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than a certain threashold 11"

Reply 1:

Thank you for your advice. As your suggestion, we have modified accordingly in the Introduction to make it easier to be understood: Specifically, the results showed that using a DPI both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than a certain threshold (60 liters/min measured at no resistance) 11.

Major concerns 2:

I also suggest that authors include the measurement of PIF rate even at hospital entry and not only at discharge during the hospitalization and they also measure the PIF rate at 60 lpm of resistance and only at 0 resistance. This can add some other information with scarce adjunctive work.

Reply 2:

According to your suggestion, we will measure PIFR R at 0 resistance (correspond to pMDI) and at Med High resistance level of InCheck DIAL® (correspond to turbuhaler®). It is worth noting that the threshold (60L/min) is determined at no resistance.

We have modified in the Method: “In this study, we set the resistance of the InCheck DIAL® both to zero (correspond to pMDI) and Med High resistance level of InCheck DIAL® (correspond to turbuhaler®) when measuring PIFR.”

We agree that measuring PIFR at hospital entry would indicate inhalation capacity at the beginning of AECOPD, but it is not the main objective of the current study. We measured this in another study.

Major concerns 3:

At last I suggest to remove the sentence "shake the device" as error for the Foster MDI as it is a solution and it does not require shaking.

Reply 3:

Thank for your suggestion. We have remove the error “patients dose not shake the device before inhaling” in Table 2.