The rescue intervention strategy for asthma patients under severe air pollution: a protocol for a single-center prospective randomized controlled trial

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Abstract
Background Asthma is a common chronic airway inflammatory disease. Exacerbation of asthma not only accelerates the progression of the disease, but also increases the incidence of hospitalization and death. Studies have shown that air pollution is a high-risk factor of exacerbation of asthma. However, there are rare treatment strategies recommended to reduce severe air pollution related exacerbation of asthma.

Methods/design This is a single-center, prospective, randomized and standard treatment parallel control clinical trial. Seventy-two asthma patients in non-exacerbation stage according to GINA guidelines 2017 will be recruited and equally assigned to Rescue Intervention Strategy (RIS) group or the control group. Original treatments for participants include unused inhaled drug, use short-acting β-agonists (SABA) on demand or use Budesonide/Formoterol (160μg/4.5μg/ dose, 1-2 dose / time, b.i.d). The rescue intervention strategy for RIS group is Budesonide / Formoterol plus the original treatment until the end of severe pollution (air quality index, AQI<200). Control group will maintain the original treatment. The intervention will last for one year. Primary outcome is the frequency of exacerbation asthma per year. And the secondary outcomes include the number of unplanned outpatient visits, emergency visits, hospitalization, medical cost and mortality caused by exacerbation asthma per year.

Discussion The rescue intervention strategy is a novel strategy for asthma management under severe air pollution. Results of the study will provide reference information to guide clinical practice in reducing the air pollution related exacerbation of asthma.

Introduction
Air pollution has been made more and more attention to the serious consequences, especially in China and other developing countries. The evidence has demonstrated that air pollution could cause critical public health problems. A retrospective study of 80 515 deaths in Beijing during 2004-2008 has found that the reduction of life expectancy was associated with increased air pollution. To be more specific, an interquartile range increase in particulate matter with aerodynamic diameter < 2.5 μm (PM$_{2.5}$), PM$_{10}$, SO$_2$ and NO$_2$ led to years of life lost increases of 15.8, 15.8, 16.2 and 15.1 years
respectively [1].

Asthma is a common chronic airway inflammatory disease. There are more than 45 million adults suffering from asthma in China [2]. Exacerbation of asthma not only accelerates the progression of the disease, but also increases the incidence of hospitalization and death. It has already been proven that air pollution could cause exacerbation of asthma [3]. Unfortunately, there are rare treatment strategies recommended to reduce severe air pollution related exacerbation of asthma. Inhaled corticosteroids (ICS) / long-acting β-agonists (LABA) with single maintenance and reliever therapy (SMART) is well known for significantly reduce exacerbation of asthma [4]. However, the relief therapy of SMART is applied when asthma patient has symptoms, which means airways have been damaged by atmospheric pollutant through inflammatory responses. And some of the ICS/LABA (such as Budesonide / Formoterol) might stop the inflammatory responses in rapid acting [5]. Therefore, we hypothesize that the rescue intervention strategy of Budesonide / Formoterol plus the original treatment until the end of severe pollution may reduce exacerbation of asthma caused by air pollution before the patient has symptoms. We will undergo a 1.5-year single-center prospective randomized controlled clinical trial to determine whether there is a difference in frequency of exacerbation asthma per year and exacerbation asthma related visits, hospitalization, mortality, costs and others between the rescue intervention strategy group and the control group.

Methods
Study design and setting

This study is a single-center, prospective, randomized and standard treatment parallel control clinical trial (see figure 1). We followed the standardized program intervention: standard protocol items recommendations for interventional trials (SPIRIT) 2013. And we followed the similar methods of Wang et al. 2019 [6], especially in ‘Intervention’ part and ‘Outcomes’ part. Patients identified at Peking University First Hospital who meet the inclusion criteria (the details are shown in ‘Inclusion Criteria’ part) and not the exclusion criteria (the details are shown in ‘Exclusion Criteria’ part) will be recruited. Then, an informed consent will be signed, and each participant visit will be overseen by a trained clinician.
At the baseline visit (V0), the participants will receive data collection including sex, age, education, income, type of medical insurance, working/home addresses, the Air Pollution Monitoring Station for Study (which is defined as the nearest air pollution monitoring station from the working place for employee or from home for non-employee), medical/surgical history, suspected allergen contact history (such as pet), therapeutic scheme of asthma, exacerbation situation in the recent three months, physical examinations (height, weight, body mass index (BMI), heart rate, blood pressure), asthma assessment scales (mini asthma quality of life questionnaire 7 (mini-AQLQ 7), numerical control questionnaire (ACQ), asthma control test (ACT) score), lung function test (bronchodilator reversibility test), and fraction of exhaled nitric oxide (FeNO).

They will be determined whether to move to the washout period (for four weeks) according to their therapeutic scheme of asthma before randomization (see Table 1). After that, the participants will be randomly divided into two groups, the rescue intervention strategy (RIS) group and the control group. Exacerbation situation in the recent three months, physical examinations, asthma assessment scales, lung function test (bronchodilator reversibility test), and FeNO will be repeated at the randomization day (V1).

Table 1 The therapeutic replacement scheme for washout period

| Therapeutic scheme before washout period | Therapeutic replacement scheme | Time of washout period |
|----------------------------------------|--------------------------------|------------------------|
| No use of inhaled medication           | Maintain the original treatment| Go directly into randomization without washout |
| Use SABA on demand                     |                               |                        |
| Use Budesonide / Formoterol (160µg/4.5µg/dose, 1-2doses/time, b.i.d) |                                |                        |
| Regular inhalation of SABA and / or LABA and / or ICS and / or anticholinergics and / or other types / doses of inhaled drugs | Budesonide / Formoterol (160µg/4.5µg/dose, 1-2 doses/time, b.i.d) | For 4 weeks Wash-out |

SABA, short-acting β-agonists; LABA, long-acting β-agonists; ICS, inhaled corticosteroids.

When air quality index (AQI) of the Air Pollution Monitoring Station for Study is more than or equal to 200, the RIS group will accept Budesonide / Formoterol (160µg/4.5µg/ dose, 1 dose / time, b.i.d) plus the original treatment until the end of severe pollution (AQI < 200). At the same time, the control group will maintain the original treatment.
Participants will be requested to visit Peking University First Hospital every 3 months until 1 year later (V2-V5). At each visit, exacerbation situation in the recent three months, physical examinations, asthma assessment scales, and lung function test (bronchodilator reversibility test) will be repeated, and FeNO will be plus only at the last visit (V5).

Inclusion Criteria
Patients will be eligible to participate if all the following criteria apply: (1) 18-80 years old, male or female; (2) asthma patients of non-exacerbation stage (according to GINA guidelines 2017); (3) quit smoking for more than or equal to 6 months, or have no smoking history; (4) have no problem in daily activities; (5) Beijing residents, the employee should make sure that there are air pollution monitoring stations within 5 km near the working place, the non-employee should make sure that there are air pollution monitoring stations within 5 km near home; (6) have smartphone at their disposal; (7) informed consent obtained by themselves; (8) willing to follow the research program.

Exclusion Criteria
Patients will not be eligible to participate if any of the following exclusion criteria are present: (1) have been diagnosed with other chronic respiratory diseases, such as chronic obstructive pulmonary disease, lung cancer, tuberculosis, bronchiectasis, and diffuse lung disease (interstitial pneumonia, occupational lung disease, sarcoidosis, etc.); (2) have the history of lobectomy, lung transplantation, or pleural disease; (3) with severe underlying disease (including severe psychiatric disorders, dysgnosia, nervous system disease, other malignant tumor, chronic liver disease, heart failure, autoimmune disease, and chronic kidney disease); (4) life expectancy is less than 3 years; (5) have no outdoor activities; (6) plan to move out of Beijing within 2 years; (7) plan to decorate home or work place during the research period; (8) alcoholism, or drug abuse; (9) allergy history or other contraindication for the medicine used in the research; (10) be participating in other clinical trials; (11) poor compliance; (12) without signing informed consent; (13) with osteoporosis and diabetes for the risk of adverse effect of using Budesonide / Formoterol; (14) the amount of cigarette smoking is
more than or equal to 10 pack-years.

Randomization and grouping

Block randomization will be used to generate random code. The random code will be designed in a 1:1 ratio (RIS group or control group), with a block size of four, using the SAS 9.2 software package (SAS Institute, Cary, NC). Based on the random number, the random grouping envelopes will be made by the people who are outsiders of the clinical trial. And the randomization results will be sealed in envelopes until the end of the study. Then, participants will be randomly assigned to the RIS group or the control group.

Intervention

After randomization and grouping, all participants will be asked to add WeChat (this is a popular social App. provided by Tencent Company, China) friends with intervention clinician. The communications between participants and intervention clinician will be mainly through WeChat App., and these data in the App. will be saved and have a back-up.

Intervention clinician will get real-time AQI by Beijing Air Pollution App. (provided by Beijing Municipal Environmental Monitoring Center, China). Intervention clinician will send real-time AQI of the Air Pollution Monitoring Station for Study to each participant by WeChat between 9 AM. to 10 AM. every day. When AQI is more than or equal to 200, intervention clinician will ask participants in the RIS group to accept Budesonide / Formoterol (160μg/4.5μg/ dose, 1 dose / time, b.i.d) plus the original treatment until the end of severe pollution (AQI < 200) by WeChat. And these participants will be reply to the intervention message to confirm by WeChat. At the same time, the control group will be asked to pay attention to protection and maintain the original treatment. The intervention will last for one year. Daily AQI and whether the intervention is successfully accomplished during every intervention period will be recorded by WeChat and will have a backup by investigator.

Follow-up and Data Collection
When participants need to visit the hospital for getting the medicine of asthma or having respiratory symptoms, they will be asked to connect with intervention clinician. Then intervention clinician will assign a clinician of our study who is working in Peking University First Hospital that day to provide medical service to participants. Medical record will be completed and saved in the Medical Record System of Peking University First Hospital. And this completed medical record will be printed immediately to preserve data. If participant visits another hospital for emergency, medical records of this visited hospital will be photographed or scanned by intervention clinician to preserve data.

Participants will be requested to visit Peking University First Hospital every 3 months until one year later (V2-V5). At each visit, exacerbation situation in the recent three months, physical examinations, asthma assessment scales, and lung function test (bronchodilator reversibility test) will be repeated, and FeNO will be plus only at the last visit (V5). The exacerbation situation will be including moderate exacerbation (which is defined as the use of reliever therapy for more than two days) and severe exacerbation (which is defined as the occurrences of unplanned outpatient visits, emergency visits and hospitalization). And the exacerbation situation will be verified by the medical records of Peking University First Hospital and other hospital. All these visits (V0-V5) and data will be recorded in case report form (CRF). The details of follow-up visits are shown in Table 2.

Table 2 Details of follow-up visits

| Screening (V0) Baseline | Randomization (V1) After washout ± 0 Day or V0 ± 0 Day | V2 3 Months ± 3 Days | V3 6 Months ± 3 Days | V4 9 Months ± 3 Days | V5 12 Months ± 3 Days |
|-------------------------|---------------------------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| Random allocation | | X | | | |
| Interventions | | | | | |
| Basic information | X | | | | |
| Alteration of basic information | | | | | |
| History of Asthma | X | | | | |
| Wash-out | X | | | | |
| Exacerbation situation | X | X | X | X | X | X | |
| Physical examinations | X | X | X | X | X | X | |
| Mini-AQLQ 7 | X | X | X | X | X | X | |
| ACQ | X | X | X | X | X | X | |
| ACT | X | X | X | X | X | X | |
| Lung function test | X | X | X | X | X | X | |
| FeNO | X | X | X | X | X | X | |
| Other medication | X | X | X | X | X | X | |
| Adverse events report | X | X | X | X | X | X | |
Clinicians and Blind Method

All clinicians took part in this clinical study will receive systemic training before the initial patient enrolment. Throughout the study, the clinicians responsible for intervention and recording the situation of randomization and grouping will be divided from the other clinicians. As a result, the others (who will be responsible for providing medical service and measuring asthma assessment scales for example) will be blinded.

Outcomes

Primary outcome is the frequency of exacerbation asthma per year, which is defined as the incidence of exacerbation asthma per patient per year.

Secondary outcomes include the number of unplanned outpatient visits, emergency visits, hospitalization, medical cost and mortality caused by exacerbation asthma per year.

Safety and adverse events

Adverse event is an unpredictable and infaust event that occurs during the study period, with or without the study intervention. In our study, all drugs used for participants are routine medicine within recommended dosage. However, adverse events may occur during daily use. All adverse events will be monitored carefully, managed promptly, and followed up until they are properly resolved, stabilized or recovered to normal. The occurrences of adverse events will be documented from the beginning to the end of the study. And the occurrences of sever adverse events will be reported to the Peking University First Hospital Institutional Review Board (IRB) as soon as possible. Severe adverse event will be analyzed every three months during the study. If there is a definite benefit ($P<0.01$) or an obvious disadvantage ($P≤0.05$), the study will be stopped after the discussion of the center and the approval of the ethic committee.
Sample Size

According to previous studies, every increase of 10 \( \mu g/m^3 \) of PM\(_{2.5} \) increased asthma related outpatients visits by 0.65%, and emergency visits by 0.49% in Beijing [7]. Every increase of 10 \( \mu g/m^3 \) of PM\(_{10} \) increased the incidence of exacerbation asthma by 3-6% [8]. The Beijing Environmental Statement published in 2014 by Beijing Environmental Protection Agency showed monthly mean concentration grew from approximately 70 \( \mu g/m^3 \) to 150 \( \mu g/m^3 \) of PM\(_{10} \), and 52 \( \mu g/m^3 \) to 150 \( \mu g/m^3 \) of PM\(_{2.5} \) [9], suggesting an increase of at least 30% risk of exacerbation with the change of air pollution. Assuming that rate ratio (RR) of exacerbation frequency for RIS group is 0.85 compared with control group, a total 60 subjects (30 for each group) are required to detect a 75% reduction of air pollution associated exacerbation at a 90% power with a two-sided significance level of 0.05. Considering a dropout rate of 20%, a total of 72 participants will be recruited in this study.

Statistical analysis

The statistical analysis will be performed with SPSS 14.0 software (International Business Machines Corp., New Your, USA). Two-tailed tests will be used in all statistical analysis, and \( P \) values <0.05 will be considered to have statistical significance (unless otherwise specified). A Poisson regression model will be used to calculate the RR of frequency of exacerbation and the 95% confidence interval will be estimated. Numeric variables will be presented as mean (standard deviation) or median (minimum, maximum; or interquartile range), And categorical variables will be presented as number of cases (percentage). Accordingly, data will be analyzed with independent sample t test, Wilcoxon rank sum test, chi-square test, continuity correction Chi-squared test or Fisher’s exact test. Characteristics of baseline will be summarized with equilibrium test. Unplanned outpatient visits, emergency visits, hospitalization, medical cost and mortality caused by exacerbation asthma per year will be compared between two groups.

Discussion
This study points out an idea about rescue intervention strategy for asthma patients under severe air pollution. This single-center, prospective, randomized and standard treatment parallel control clinical trial is aiming to figure out whether the rescue intervention strategy will reduce the air pollution related exacerbation asthma.

ICS and LABA are highly recommended by GINA for asthma patient [10]. Although long-term inhalation of ICS is a high risk of pneumonia, there is no consensus on withdrawal of ICS from asthma treatment. Compared with Salmeterol/Fluticasone, recent research showed that Budesonide/Formoterol had lower risk of adverse events [11]. Jenkins et al. demonstrated that high-dose Budesonide/Formoterol (1280μg/36μg/day) was effective and well tolerated in asthma patients [12]. In our study, the rescue intervention strategy is Budesonide / Formoterol (160μg/4.5μg/ dose, 1 dose / time, b.i.d) plus the original treatment until the end of severe pollution (AQI < 200). The maximal dose of Budesonide/Formoterol per day during the study is less than the dose of Jenkins’ research. Budesonide/Formoterol shows rapid-acting effects in asthma and can be used for maintenance and reliever therapy in single-inhaler [13]. And the SMART study reported that receiving Budesonide/Formoterol might significantly reduce exacerbation of asthma [4]. As a result, Budesonide/Formoterol is believed to be an ideal rescue intervention drug and might be safe for adding to the original treatment. For the sake of decreasing the effects of different inhaled drugs, original treatment of participants in our study will be selected from no use of inhaled medication, use SABA on demand or use Budesonide/Formoterol (160μg/4.5μg/ dose, 1-2 dose / time, b.i.d).

The article of Wang et al. 2019 [6] is the protocol of the chronic obstructive pulmonary disease (COPD) associated study which is leading by our department (Department of Respiratory and Critical Care Medicine, Peking University First Hospital). And these two studies share some same research-members such as Guangfa Wang and Tianyu Zhou. However, it’s quite different in assessment scales, therapeutic replacement scheme for washout period, inclusion and exclusion criteria, randomization, grouping, and etc. which are suitable for asthma and single-center study but not for COPD and multi-center study. Moreover, there are several differences between the ‘Intervention’ part methods of these two studies. First, our study uses real-time AQI instead of 24-h mean AQI, and the rescue
The intervention strategy of our study will be performed until the end of severe pollution (AQI < 200) instead of the third day after the end. HEART study found that air pollution led to delayed inflammatory burst in lung lasting almost three days and airway inflammation of COPD patients get worsen after exposure to severe air pollution [14, 15, 16]. Nevertheless, our study uses real-time AQI and might start the intervention program in the first few hours when severe air pollution begins. This strategy might stop the inflammatory responses in an early stage to protect airways against damage from atmospheric pollutant. What’s more, recent studies have suggested a possible association between respiratory tract infection and the use of ICS in asthma patients [17]. The strategy we used will decrease the dosage of ICS to reduce the risk. Second, the communications between participants and intervention clinician will be mainly through WeChat App. in our study. WeChat is the most popular social App. in China [18]. The use of WeChat is both customary to improve participant compliance and objective to ensure the authenticity of data.

The limitations of our study are as follows. First, the study is not a double-blind design because participants will know treatment which will be administered. To decrease the potential bias, investigators after randomization (who will be responsible for providing medical service and measuring asthma assessment scales at the follow-up visits for example) will be not informed of the administration of participants. Second, the study is not a multi-center design and only performed in Beijing. That will affect the evidence grade classify of our study.

Conclusions
This is a single-center, prospective, randomized and standard treatment parallel control study aiming at reducing air pollution related asthma exacerbations. Evidence of the study will provide effectiveness and safety for a novel and precise strategy call the rescue intervention strategy.

Trail status
This document is based on version 1.2 (Nov 11, 2018) of the study protocol. The recruitment has finished (from 2019-1-1 to 2019-6-30), and the trial is currently at the stage of participant follow-up visits and data collection (from 2019-1-1 to 2020-6-30).
Abbreviations
AQI: air quality index; ICS: inhaled corticosteroids; LABA: long-acting β-agonists; RIS: Rescue Intervention Strategy; SABA: short-acting β-agonists; SMART: single maintenance and reliever therapy; SPIRIT: standard protocol items recommendations for interventional trials; BMI: height, weight, body mass index; mini-AQLQ 7: mini asthma quality of life questionnaire 7; ACQ: numerical control questionnaire; ACT: asthma control test; FeNO: fraction of exhaled nitric oxide; CRF: case report form; IRB: institutional review board; PM: particulate matter; RR: rate ratio; GCP: Good Clinical Practice.

Declarations

Contributors
XY is joint first author. JH obtained funding. GW and JH are joint corresponding authors. GW and JH conceived and designed the study. JH, XY, YH and TZ drafted the protocol. JH, XY, and YH conducted data collection. JH, XY, CG and XW conducted data management and statistical analysis. ZY conducted administrative management. All authors read and approved the final manuscript and are responsible for their contributions.

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Data Availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval and consent to participate
The first version study protocol has been approved by the Peking University First Hospital Institutional Review Board (IRB) (2018[268]) on Dec., 2018. Any protocol modifications will be submitted for the IRB review and approval.

The study will be conducted in accordance with Good Clinical Practice (GCP) requirements and ethical principles of the Declaration of Helsinki.

The purposes, procedures, as well as potential benefits and risks of the study will be explained carefully by investigators with a written informed consent. Written informed consent will be obtained from each participant. Personal information and related documents of all participants will be kept strictly. Every participant will be identified by a subject number and a name acronym in the Case Report Form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
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