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CLINICAL TRIAL PROTOCOL

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A double-blind randomized controlled trial of N-acetylcysteine (NAC) for the treatment of acute exacerbation of chronic obstructive pulmonary disease

Wang Chung Kwok | **Shung Kay Samuel Chan** | **Ka Yan Chiang** | **Chung Man James Ho**

Division of Respiratory Medicine, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Correspondence
Chung Man James Ho, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Professorial Block, 102 Pokfulam Road, Hong Kong.
Email: jhocm@hku.hk

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with acute exacerbation (AECOPD) being a common sequalae which negatively impact health status, rates of hospitalization and readmission, and disease progression. N-acetylcysteine (NAC) has been studied in COPD in both stable state and acute exacerbations, which has been shown to have small beneficial effects in stable COPD, as well as AECOPD. Yet, there has been lack of study with well-designed protocol to assess the role of NAC in more objective outcomes in AECOPD.

Methods: This is a double-blind randomized controlled trial. Patients will be randomized in 1:1 ratio to receive oral NAC at 600 mg twice daily or placebo twice daily with standard of care. Partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2) will be measured on days 1 and 7. The following will be measure at baseline and on day 4 and 7: Forced expiratory volume in one second (FEV_1), 24-hour sputum volume, oxygen saturation (SaO_2), end-tidal CO_2, Leicester Cough Questionnaire (LCQ) score, COPD Assessment Test (CAT) score, grading of wheeze and grade of dyspnoea; blood inflammatory markers (leucocyte count, neutrophil count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and high sensitivity CRP (hs-CRP)). Patients will be randomized to oral NAC at 600 mg twice daily or placebo for 7 days. The main outcome measures include: The difference in PaO_2 on day 7. Secondary outcome: Change in following parameters on day 4/7 from baseline: FEV_1, sputum volume, CAT score, LCQ score, SaO_2, grade of wheeze; mMRC Dyspnoea Scale, end-tidal CO_2, blood inflammatory marker, change in PaO_2/FiO_2 ratio from baseline to day 7, $PaCO_2$ on day 7, 28 and 90 days' mortality, time to wean off supplemental oxygen, length of stay.

Primary and secondary outcomes will be compared among the two treatment groups with two-sample *t*-test.

Discussion: We hypothesize that NAC use in COPD exacerbation can provide benefits in clinical and laboratory parameters.

Trial Registration: ***Name of the registry***: ClinicalTrials.gov
Trial registration number: NCT05706402.

URL of the trial registry record for this trial: https://classic.clinicaltrials.gov/ct2/show/NCT05706402
Date of registration: Registered on 11th January 2023
Funding of the trial: The Health and Medical Research Fund (HMRF).
Name and contact information for the trial sponsor: Wang Chung Kwok, Clinical Assistant Professor, Honorary Associate Consultant, Queen Mary Hospital, The University of Hong Kong, Hong Kong.
Role of sponsor: The funder is not involved in the planning of the study, gathering, analysing, and interpreting the data, or in preparing the manuscript.

KEYWORDS
COPD, COPD exacerbation; N-acetylcysteine; RCT

INTRODUCTION

Background and rationale

Chronic obstructive pulmonary disease (COPD) is a major chronic lung disease resulting in airflow limitation. Patients with COPD experience gradually deteriorating lung function, which may be complicated by acute exacerbations.[1]

COPD is currently ranked as the fourth leading cause of death worldwide according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[2] The Global Burden of Disease Study estimated that 3.2 million people died from COPD in 2015, an increase of 11.6% compared with 1990. During the same period, the prevalence of COPD also increased by 44.2% to 174.5 million in 2015.[3]

The prevalence rates of COPD in Hong Kong for older adults aged ≥60 years were reported to be 25.9% and 12.4% based on two different spirometric definitions (post-bronchodilator FEV_1/FVC <70% or lower limit of normal range). The crude mortality rate of COPD in Hong Kong was 29.1/100,000, whereas the crude hospitalization rate was 193/100,000 in 2005.[4] This disease accounted for over 30,000 inpatient discharge cases and deaths in 2016 and 1223 registered deaths in 2017.

An exacerbation of COPD is defined as an acute worsening of respiratory symptoms resulting in the need for additional therapy. The most common cause of acute exacerbation is respiratory tract infection, which can be categorized into mild, moderate, and severe, depending on the treatment required. Exacerbations of COPD are important events in the management of COPD, because they negatively impact health status, rates of hospitalization and readmission, and disease progression.[2,4–6]

N-acetylcysteine (NAC) is frequently used in patients with COPD as a mucolytic. Besides its mucolytic effects, high-dose NAC has additional benefits in patients with stable COPD, including improving lung function and reducing exacerbations. The benefits of NAC in COPD are related to its antioxidant properties.[7] Taken orally, NAC is deacetylated to cysteine, leading to increased concentrations of reduced glutathione in the plasma and airways.[8,9] Studies on the dose-dependent effects of NAC in COPD patients showed a high dose of NAC was needed to achieve its antioxidant effects and clinical benefits in COPD patients, whereas a dose of 600 mg once daily was not able to increase glutathione levels.[10] According to a study conducted in Hong Kong on patients with stable COPD, 1 year of treatment with high-dose NAC at 600 mg twice daily improved small airways function in terms of forced expiratory flow from 25% to 75% and forced oscillation technique, and also significantly reduced exacerbation frequency with a decreasing trend in admission rate.[11] In a meta-analysis, patients treated with NAC had significantly and consistently fewer exacerbations of COPD.[12]

The role of NAC was examined in a Delphi consensus study involving 53 COPD experts from 12 countries.[13] Respondents agreed that regular treatment with mucolytic agents could effectively decrease the frequency of exacerbations and the duration of mild-to-moderate exacerbations, while delaying the time to first exacerbation and increasing symptom-free time in COPD patients. Moreover, they concurred that NAC could improve the efficacy of some classes of antibacterial drugs and was effective as a short-term treatment for the symptoms of acute exacerbations when combined with other drugs. The panel in the Delphi consensus study also approved the doses of NAC with favourable side effect profiles to be recommended for regular use in patients with a bronchitic phenotype.

However, there have been conflicting results regarding the efficacy of NAC for treating acute exacerbation of COPD. A double-blind, double-dummy, placebo-controlled randomized study in 123 patients experiencing an acute exacerbation of COPD suggested treatment with NAC 1200 mg/day could improve biological markers and clinical outcomes.[14] However, the primary outcome in this study was the change in inflammatory markers, which are also affected by the cause of the exacerbation. Moreover, changes in inflammatory makers may not have significant clinical and physiological implications. In addition, antimicrobial treatments can also be another cofounding factor. Another small-scale study on 40 patients found the NAC group showed significant improvements in the mean partial pressure of oxygen (PaO_2) on days 3 and 7, and partial pressure of carbon dioxide ($PaCO_2$), and oxygen saturation (SaO_2) on day 7; the clinical signs including wheezing and dyspnoea; and the need for nasal oxygen support.[15]

On the other hand, another double-blind trial randomly assigned 50 patients with COPD exacerbation to receive NAC (600 mg, twice daily) or placebo for 7 days. They found there were no differences in the rate of change of forced expiratory volume in 1 second (FEV_1), vital capacity, oxygen saturation, breathlessness, or length of hospital stay between the two groups.[16–18] However, this study had a small sample of only 25 subjects in each group and also focused on parameters that might not reflect the situation in COPD acute exacerbation such as FEV_1 and vital capacity, while other important parameters such as cough score, sputum volume, and mortality on discharge were not assessed. Negative results were reported in a placebo-controlled study,[19] which included patients with severe COPD and increased sputum production who were hospitalized for an exacerbation. Subjects were randomized to receive either NAC 200 mg three times daily or placebo in addition to their usual treatment. They found significant improvements in the ease of sputum production, dyspnoea at rest and on exertion, FEV_1, and PaO_2 in both NAC and placebo groups, with no difference between the two groups. The dose of NAC used in this study was below the level needed to affect glutathione levels, which may account for the lack of difference in the observed benefits in these two groups. Despite the potential benefits of NAC in COPD exacerbation, NAC has not been included as an adjunct for the treatment of COPD exacerbation in international guidelines. A possible explanation could be related to the contradicting results from various studies. In the largest scale study conducted so far, the change in inflammatory markers was the primary outcome, whereas the clinical outcomes were the secondary outcomes.[14] Other studies that used clinical outcomes as the primary outcome of interest had rather small sample sizes, and these studies showed inconsistent results. A dedicated study focusing on objective clinical and physiological outcomes is urgently needed. As NAC is relatively low cost, readily available, and has a favourable side effect profile as a treatment for COPD exacerbation, it is important to properly assess the clinical benefits of NAC as an adjunct to standard medical treatments to hasten recovery.

Hypotheses

The use of NAC in acute COPD exacerbation can improve physiological parameters, symptoms, lung function, reduce blood inflammatory markers, and length of hospital stay.

Objective

This study will assess the role of NAC in the treatment of acute COPD exacerbation in terms of clinical, physiological, and laboratory parameters, including PaO_2, PaO_2/FiO_2 ratio, $PaCO_2$, SaO_2, end-tidal CO_2, length of stay, coughing, wheezing, dyspnoea, need for supplemental oxygen sputum volume, FEV_1, and blood inflammatory markers.

Trial design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional	
Study Model:	Parallel Assignment
	This study is a double-blind randomized controlled trial on NAC as an adjunctive treatment for acute COPD exacerbation. The randomization will be done via computer software with half of the patients randomized to receive oral NAC (600 mg twice daily) and half receive placebo, with randomization ratio being 1 to 1. Patients in the two randomized group will be asked to participate in the study for a maximum of 1 week.
Number of Arms:	2
Masking:	Double (Participant, Investigator)
Allocation:	Randomized
Enrolment:	80 [Anticipated]

METHODS

Subjects (with justification on sample size)

This clinical trial will be conducted at the Department of Medicine, Queen Mary Hospital. The Division of Respiratory Medicine at Queen Mary Hospital is a tertiary referral centre serving the entire territory and is the major receiving unit for patients with various respiratory diseases (including COPD) in the Hong Kong West Cluster. Based on hospital admission records in the past 12 months, there were on average 77 patients with acute exacerbation of COPD admitted to the general medical ward every month. Potential study subjects will be recruited from general medical and respiratory subspecialty wards based at Queen Mary Hospital. The following eligibility criteria will apply.

Inclusion criteria:

1. Aged 40 years or above, either male or female.
2. Patients who are current or ex-smokers
   a. Ever-smoker is defined as having smoked at least one cigarette, pipe, water pipe, cigars, or hand rolled cigarettes a day for 1 or more years.
3. Patients with a pre-existing diagnosis of COPD admitted to the general medical and respiratory subspecialty wards for acute COPD exacerbation
   a. COPD is defined as dyspnoea and/or chronic productive cough with spirometry confirmation of persistent airflow limitation at FEV1/FVC less than 70%.
   b. COPD acute exacerbation is defined as an acute increase in symptoms (one or more of the following: cough frequency and severity, sputum production,

dyspnoea) beyond normal day-to-day variations leading to a change in medication.
4. Patients who consent to join this clinical trial

Exclusion criteria:

1. Patients who are on long-term NAC treatment
2. Patients who are not able to take NAC including drug allergy
3. Patients with other co-existing respiratory diseases including but not limited to asthma, interstitial lung diseases, and bronchiectasis
4. Patients on non-invasive or invasive mechanical ventilation where oral medication is not allowed.
5. Patients on long term macrolide treatment
6. Patients on macrolide as antibiotics for COPD exacerbation

Outcome measurement

The co-primary endpoint of interest is the difference in mean PaO_2 on day 7 of treatment and the change of PaO_2 from day 0 to day 7. The secondary outcomes include treatment change in PaO_2/FiO_2 ratio from baseline to day 7, sputum volume on days 4 and 7, CAT score on days 4 and 7, LCQ score on days 4 and 7, grade of wheeze on days 4 and 7, grade of dyspnoea on the modified Medical Research Council (mMRC) Dyspnoea Scale on days 4 and 7, FEV_1 on days 4 and 7, end tidal CO_2 on days 4 and 7, SaO_2 on days 4 and 7, $PaCO_2$ on day 7, time to wean off supplemental oxygen, length of stay, blood inflammatory markers, and 28- and 90-day mortality.

Sample size calculation

The sample size calculation is based on the primary outcome, i.e. the difference in mean PaO_2 on day 7 of treatment. The calculation is based on previously reported results in the literature.[15] In a single-centre, prospective interventional study on the role of NAC in COPD exacerbation, the mean PaO_2 was 93.5 ± 3.5% in the NAC group and 90.1 ± 4.8% in the placebo group (p-value = 0.01).[20] For a 90% power to detect a difference in means between matched pairs using a two-sided type I error of 0.05, a sample size of 80 subjects (40 patients in each treatment group) will be needed. We assume the mean difference is 3.4 with standard deviations of 3.5 and 4.8 from the two groups. The calculation is based on a two-sided two-sample unequal-variance t-test.

The data will be analysed with intention to treat (ITT) analysis and per-protocol analysis, with inclusion of non-compliant patients in the ITT analysis.

From 2015 to 2019, the monthly average number of admissions for acute exacerbation was 77 (ranging from 66 to 89 per month over the years). Based on the previous admission records, we expect 25% of these patients will be readmissions, 25% will have co-existing respiratory diseases, 10% will require mechanical ventilator support, 10% may not be able to consent to the trial, and none will be on long-term NAC treatment, resulting in about 20 eligible patients. Considering the inclusion and exclusion criteria as listed above, we aim to recruit an average of five eligible subjects every month. Participants who fail to complete the 1-week NAC or placebo treatment due to withdrawal of consent, adverse effects, deterioration requiring mechanical ventilator support and unable to continue oral medications, and those who are unable to comply with the study procedures and decided to quit the study will be replaced in order to reach our target of 80 subjects. Allowing for 15% drop-out rate, the study recruitment should be completed in around 18 months. Potential reasons for drop-out include failure to perform the study procedures, significant adverse events from the study treatment resulting in discontinuation, and deterioration requiring mechanical ventilator support and unable to continue oral medications.

Methods

PaO_2, $PaCO_2$ and PaO_2/FiO_2 ratio

PaO_2 and $PaCO_2$ on day 7 of treatment will be measured by arterial blood gas. The PaO_2/FiO_2 ratio will be calculated by dividing the arterial oxygen partial pressure (PaO_2 in mmHg) by the fractional inspired oxygen.

PaO_2, $PaCO_2$ and PaO_2/FiO_2 are the objective parameters that assess the patients' respiratory status. They have been used to define the development of respiratory failure. PaO_2 and $PaCO_2$ are the gold standard in determining the oxygenation and ventilation status of the patients. PaO_2/FiO_2 have been incorporated in various scoring system as a marker of respiratory failure severity, including Acute Physiology and Chronic Health Evaluation (APACHE) IV, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score II (SAPS-II) and SAPS-III, '*S*ystolic blood pressure, *M*ultilobar infiltrates, *A*lbumin, *R*espiratory rate, *T*achycardia, *C*onfusion, *O*xygen, and *pH*' (SMART-COP) risk score and Berlin definition of Acute Respiratory Distress Syndrome (ARDS). They are also being frequently used in clinical studies as the outcomes of successful treatment in various respiratory diseases. By measuring PaO_2 and $PaCO_2$ and PaO_2/FiO_2, we could have objective assessment of the benefits of NAC in terms of physiological improvement.

End-tidal CO_2 and SaO_2

End-tidal CO_2 will be measured using Capnostream™ 35 Portable Respiratory Monitor. It allows non-invasive, real-time respiratory status monitoring of $etCO_2$, SaO_2, respiration rate, and pulse rate. The device measures respiratory gas via nasal by aspirating a small sample from the exhaled breath through the cannula tubing to a sensor located inside the monitor.

End-tidal CO_2 and SaO_2 are objective parameters to assess the respiratory status of the patients. They have the benefits of being non-invasive and easily repeatable. They can be used as longitudinal follow up of the patients throughout the treatment course. They are also being frequently used in clinical studies as the outcomes of successful treatment in various respiratory diseases. End-tidal CO_2 was shown to have good correlation of $PaCO_2$ level in patients with COPD. SaO_2 is one of the commonest bedside assessment tools for the oxygenation level of the patients By measuring end-tidal CO_2 and SaO_2, we could have objective assessment of the benefits of NAC in terms of physiological improvement.

Sputum volume

Sputum volume will be measured by a standard sputum bottle. Increase in sputum volume is considered to be a hallmark of COPD exacerbation.[21] Measurement of change in sputum volume can provide a simple assessment of the clinical improvement of COPD exacerbation at low cost.

CAT score, LCQ score, grade of wheeze and grade of dyspnoea on the modified Medical Research Council (mMRC) Dyspnoea scale

CAT score and grade of dyspnoea on the mMRC Dyspnoea Scale are the most commonly used scoring system in COPD.[22] The change in the values have been shown to correlate well with the respiratory status of COPD. They are also included in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendation as the tool to assess the symptom burden.

LCQ have been studied in During COPD Exacerbation Convalescence. Literature suggested that cough frequency falls significantly during the convalescent period following an COPD exacerbation.[23] LCQ can serve as a marker to assess the symptomatic improvement in COPD exacerbation.

The mMRC Dyspnoea Scale, CAT score, LCQ score will be completed by subjects with the help from PI or Co-I or their delegates if needed.

Grade of wheeze, to be assessed by the PI or Co-I, is a simple bedside assessment that can assess the severity of COPD.[24] This could allow a simple assessment of the respiratory status for the patients with COPD exacerbation.

FEV_1

FEV_1 will be measured by portable spirometer. FEV_1 is the gold standard of lung function measurement and is also a criteria to diagnose COPD. FEV_1 is one of the common outcomes in various COPD clinical trials. The measurement of FEV_1 can provide objective assessment of the respiratory physiology of the patients with NAC treatment.

Time to wean off supplemental oxygen, length of stay

Time to wean off supplemental oxygen and length of stay are the simple yet objective markers of clinical improvement with COPD treatment. They also correlate well with the health care costs.

28- and 90-day mortality

28- and 90-day mortality are the objective parameters to assess the survival of the patients after COPD exacerbation.

The timepoints of conducting the assessments for each visit is shown in Table 1.

Study design

This is a double-blind randomized controlled trial on NAC as an adjunctive treatment for acute COPD exacerbation. Eligible subjects with COPD will be identified from either the general medical ward or the respiratory subspecialty ward at the Department of Medicine, Queen Mary Hospital. Details of the study will be explained to potential subjects by the PI or his designee before obtaining written informed consent. COPD exacerbation was defined as an event characterized by dyspnea and/or cough and sputum that worsens over ≤14 days.[25,26] Mild exacerbations were defined in patients treated with short acting bronchodilators (SABD) only. Moderate exacerbations were defined in patients who were treated with SABDs and oral corticosteroids ± antibiotics. Severe exacerbations were defined in patients that required hospitalizations or visit to the emergency room.[25] At the first visit, detailed history taking, physical examination, and baseline assessments (body weight, body height, body-mass index, complete blood count, liver function test, renal function test, arterial blood gas, and chest x-ray) will be performed. Baseline assessments will include PaO_2, PaO_2/FiO_2 ratio, $PaCO_2$, 24-hour sputum volume, SaO_2, end-tidal CO_2, cough score by Leicester cough questionnaire (LCQ), COPD Assessment Test (CAT) at 24 h after admission, grade of wheeze, dyspnoea by mMRC Dyspnoea Scale, and lung function test by the portable spirometer. Blood inflammatory markers including white cell count, neutrophil count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and high-sensitivity CRP (hs-CRP) will also be measured, total 20 mL of blood will be taken. The blood tests arranged for the patients are the basic blood tests for clinical management of COPD exacerbation and it does not involve extra blood testing for the patients. Patients in both treatment and placebo groups will receive identical standard of care for COPD acute exacerbation including oral prednisolone 30 mg daily for 1-week (With concomitant pantoprazole 40 mg daily [if not on proton pump inhibitor before the admission] and potassium chloride 600 mg twice daily

TABLE 1 Timepoints of conducting the assessments for each visit.

	24 h after admission	Day 4 of hospitalization	Day 7 of hospitalization
Informed consent	x		
Demographic and baseline characteristics	x		
Medical history	x		
Inclusion/exclusion	x		
Vital signs	x	x	
Concomitant medications	x	x	x
Randomization	x		
Leicester cough questionnaire (LCQ)	x	x	x
mMRC Dyspnea scale	x	x	x
Grade of wheeze	x	x	x
COPD Assessment Test (CAT)	x	x	x
Sputum volume in last 24 h	x	x	x
Oxygen saturation	x	x	x
Carbon dioxide level from exhaled breath (End tidal CO_2)	x	x	x
Arterial blood gas	x		x
Lung function test	x	x	x
Saving blood sample for inflammatory markers	x	x	x
Adverse events	x	x	x

[Omitted if blood potassium level is above upper limit of normal]), inhaled salbutamol four puffs every 4 h for 1 week, and antibiotics with oral Amoxicillin/Clavulanic acid 1 gram twice daily according to the standard treatment order form. Alternative antibiotics can be used if patients have allergy or contraindications, and it will be decided by the PI or Co-I. The usual inhalers and oral medications for COPD will be continued. The patients will also be prescribed with the necessary medications for symptomatic relief. For mucolytics, both patients in the treatment and placebo group will be prescribed with mucolytics that do not contain NAC such as bromhexine, cyclidrol or ambroxol if needed. Patients recruited into the study will be taken to the Respiratory ward in Queen Mary Hospital for further care. Subjects fulfilling the selection criteria will be randomized in a 1:1 ratio to receive either oral NAC at 600 mg twice daily or placebo (identical appearance and similar taste) twice daily for 7 days. Randomization will be done by computer program. Randomization will be stratified according to disease severity at enrolment. Mild disease is defined as those not needing supplemental oxygen, whereas moderate disease is defined as those who need supplemental oxygen but not ventilator support. The NAC or placebo treatments will be delivered to the ward by the Pharmacy Unit after the designated drug prescription form has been signed by the Principal Investigator [PI]/Co-Investigators [Co-Is]. The NAC or placebo treatments will then be given by ward nurses who will be blinded to the treatment arm. A specific item code for NAC or placebo will be prepared by the pharmacy department of Queen Mary Hospital. Placebo with identical taste and appearance will be prepared by Zambon Pharma. Arterial blood gas will be checked on days 1 and 7 for PaO_2 and $PaCO_2$ value, as well as to calculate the PaO_2/FiO_2 ratio. The 24-h sputum volume, SaO_2, end tidal CO_2, LCQ score, grade of wheeze, CAT score, and dyspnoea by mMRC Dyspnoea Scale will be carried out by blinded research assistants, the PI, or Co-Is and repeated on days 4 and 7. Blood inflammatory markers including white cell count, neutrophil count, ESR, CRP, and hs-CRP will be measured on days 4 and 7. Lung function test by portable spirometer will be performed on days 1, 4 and 7. Time to wean off supplemental oxygen, length of hospital stay, and 28- and 90-day mortality will be recorded.

Subgroup analysis will be performed on patients with COPD exacerbation with different severity.

For patients who have hospital stay less than 7 days, the day 4 and 7 assessment will be performed in out-patient setting with ward follow up arranged in B6 ward for them. The NAC and placebo, together with other treatment for COPD exacerbation will be provided to the patients upon discharge. As such, this would not lead to any lengthening of the length of stay.

Any adverse events will be recorded according to the Common Terminology Criteria for Adverse Events [CTCAE] version 5.

Sequence generation

The randomization was performed by Research Electronic Data Capture (REDCap) version V13.8.1. The randomization

list is held by a blinded investigator not involved in the subject assessment. The allocation sequences will be concealed from the investigators who are involved in subject recruitment and assessment.

Data from local cohort

We have conducted a retrospective study (unpublished) on all patients admitted for COPD acute exacerbation to Queen Mary Hospital in 2019. None of the patients were treated with long-term NAC for COPD. There was a total of 841 patients included in this study. Patients receiving NAC showed a significantly delayed time to the next admission for COPD exacerbation compared with those not receiving NAC (370.5 ± 43.9 days vs. 219.1 ± 30.0 days, $p = 0.005$), with an absolute difference of 151.4 days. The length of stay, however, was not significantly different between the two groups (2.33 ± 0.265 days vs. 2.03 ± 0.114 days, $p = 0.301$). There was a trend towards lower mortality rate among those administered NAC (1.5% vs. 3.0%, $p = 0.158$). The results from our unpublished data suggest NAC have potential benefits on COPD exacerbation. However, this retrospective study had potential limitations including that patients were prescribed different doses of NAC for varying durations. In order to properly investigate the benefits from NAC, a well conducted prospective study is warranted.

From a joint prospective clinical study by Queen Mary Hospital and Grantham Hospital including 300 patients with COPD, none of the included COPD patients were managed on long-term NAC. This study is still ongoing, and the results have not yet been published. The patients followed up in Queen Mary Hospital and Grantham Hospital reside in Hong Kong Central, West, and Southern districts, which contribute to the vast majority of patients with COPD exacerbation attending Queen Mary Hospital.

Data processing and analysis

For the primary endpoint of interest, that is, the difference in mean PaO_2 on day 7 of treatment, it will be compared among the two treatment groups by two-sample t-test. The change in the measures (PaO_2/FiO_2, $PaCO_2$, sputum volume, FEV_1, SaO_2, LCQ score, CAT score, end tidal CO_2, grade of wheeze mMRC Dyspnoea scale, blood inflammatory markers, time to wean off supplemental oxygen, and 28- and 90-day mortality) will be tested using a two-sample t-test. For results that do not follow normal distribution, non-parametric Wilcoxon signed-rank test will be used instead. Clinical characteristics of patients will be tabulated. For categorical outcomes, they will be compared by Chi-square (χ^2) test if they have normal distribution while Mann–Whitney *U* will be used if the outcomes do not follow normal distribution. The demographic and clinical data will be described in actual frequency or mean ± SD, or median and interquartile range where appropriate. Baseline demographic and clinical data will be compared between two treatment groups by independent t-test or non-parametric tests where appropriate. Multiple linear regression modelling will be used to take into account potential confounders (age, gender etc.). A *p*-value of <0.05 will be considered statistically significant. All the statistical analyses will be performed using the latest version of SPSS statistical package.

Potential hazards to subjects in the study

The subjects will need extra blood taking for arterial blood gas on day 7. The reported major complication rate from arterial puncture for arterial blood gas within 7 days was 0.14%,[27] which include embolisms or thrombosis, aneurysms, nerve damage and arteriovenous fistulas. In general, arterial puncture for arterial blood gas is considered to be a low-risk procedure with major complication rate of 0.14% only.

Confidentiality and use of results

The demographic and clinical data collected from study subjects will be stored securely at the study site, with access by the principal investigator or designated research staff. All collected data will be stored in computers locked in PI's office. All data files will be encrypted and confidential information (e.g., Hong Kong Identification Card (HKID) numbers) will be replaced with study numbers in the dataset. These data will only be used for the study as outlined in this protocol and individual patient's identity will be removed after completion of statistical analyses. No personal particulars will be included in all future scientific reports generated from this study. All data files will be deleted 5 years after completion of the study. We will ensure the compliance with ICH-GCP.

Data monitoring

The data monitoring committee consists of the co-authors of this study protocol, who are all independent from the sponsor of the study and have no competing interests. The members of the data monitoring committee also are not involved in the subject recruitment and assessment. The trial will be stopped once the planned subject number was reached, no adverse events or unintended effects are expected. The data monitoring committee will also monitor study safety outcomes.

DISCUSSION

We hypothesize that NAC use in COPD exacerbation can provide benefits in clinical and laboratory parameters.

Trial status at submission

Recruiting; Actual study start date: 2023-09-18; Estimated recruitment completion date: 2024-12-31.

AUTHOR CONTRIBUTIONS

Kwok WC will be responsible for patient recruitment, patient assessment and management. He will also be responsible for data collection, data analysis and interpretation. He will also be responsible for manuscript preparation. Chan SK and Chiang KY will be responsible for patient assessment and management, as well as data collection. Ho JCM will be responsible for site coordination, supervision of the study, manuscript preparation and review.

FUNDING INFORMATION

The study is funded by from the Health and Medical Research Fund (HMRF).

CONFLICT OF INTEREST STATEMENT

There will be no conflict of interests from both the department and any of the investigators involved. Ka Yan Chiang and Chung Man James Ho are Editorial Board members of Respirology Case Reports and co-authors of this article. They were excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The data will be available by presenting in the final manuscript, once the study data have been collected.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW22-710).

ORCID

Wang Chung Kwok https://orcid.org/0000-0002-5611-1637
Ka Yan Chiang https://orcid.org/0000-0001-8409-3352
Chung Man James Ho https://orcid.org/0000-0003-4499-5284

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