Routine (7 days) vs. clinically indicated change of the noninvasive ventilator circuit for prevention of hospital-acquired pneumonia: Protocol for a randomized controlled trial in 2 tertiary hospitals

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Abstract

Background The change frequency of the ventilator circuit was once thought to be the main cause of ventilator-associated pneumonia (VAP), but recent evidence has shown that it is not strongly relevant to VAP in invasively ventilated patients. However, circuits of noninvasive positive pressure ventilation (NPPV) are still routinely (every 7 days) changed in many hospitals to prevent hospital-acquired pneumonia (HAP) without evidence, which is a heavy economic burden on the health system. Methods This is a nonblinded, prospective, randomized controlled multicenter trial. Patients who receive NPPV onset in this hospitalization will be screened for eligibility. A total of 340 eligible participants will be stratified (3:2) in two research sites and will be randomly allocated to routine changes in the ventilator circuit group or clinically indicated changes in the circuit group at a ratio of 1:1. Routine prevention for HAP will be provided in both groups. The primary outcome is the occurrence of HAP 48 hrs after NPPV therapy starts or 48 hrs within weaning from NPPV. Secondary outcomes include the length of hospital stay, length of each circuit duration, NPPV treatment days, intubation, mortality and direct cost of the circuits and antibiotics. The growth curve of microorganisms in the ventilator circuit will also be analyzed. It is hypothesized that there will be no difference in the occurrence of HAP in the two arms. Furthermore, a decrease in circuit cost is expected in the intervention group, and the microorganisms in the ventilator circuit are predicted to not increase over time. Discussion NPPVs are widely used in patients with various diseases from different healthcare settings. Evidence-based rules for changing NPPV circuits are limited. If supported, our pioneer study will provide a cost-effective NPPV management method without increasing the risks of HAP.

Background

Noninvasive positive pressure ventilation (NPPV) is a common respiratory therapy that has been widely used in large populations in ICUs, respiratory disease departments and palliative settings. It is used for continuous respiratory support in chronic disease; early prevention of intubation in acute lung disease, such as ARDS; and is an effective weaning strategy for invasive mechanical ventilation (IMV).

Compared with IMV, NPPV has a lower (2–4) prevalence of hospital-acquired infection (HAI) due to its nature of being noninvasive. Although its rate is relatively low, hospital-acquired pneumonia (HAP) does occur with NPPV(7). Nosocomial pneumonia, including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), accounts for 21.8%(8) of HAIs and is the second most common nosocomial infection(9). HAI is associated with increases in the length of hospital stay, usage of antibiotics, morbidity, health care costs and even mortality(9, 10). Among NPPV patients, the prevalence of HAP ranges from 0–41%(2, 5). Previous studies(5) showed that nosocomial pneumonia was an independent risk factor for intubation and death in NPPV patients. A reduction in HAI would directly benefit patients and the whole healthcare system. In many hospitals in China, the rule is a 7-day circuit change(5) in the NPPV population, simply following the now-abolished norm from the IMV population, in an attempt to decrease the risks of HAP. In the past, the circuit of IMV was recommended to be changed...
routinely (every 2 days or every 7 days) to decrease the occurrence of VAP, but this was found to be unnecessary.

It should be clarified that HAP and VAP are two different complications in hospitals because they have different pathogeneses(4, 10). The American Thoracic Society(11) defined HAP as “a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission” and defined VAP as “pneumonia occurring more than 48 hrs after endotracheal intubation”. These two definitions were also accepted by the Chinese Thoracic Society(10). The main pathogenesis of VAP in intubated patients is the movement of contaminated oropharyngeal secretions(12, 13) or gastric aspiration into the lungs(14). The critical passage for secretion down to the lower respiratory tract is outside the tube between the tube cuff and the inner wall of the trachea(15). To solve this issue, various methods are utilized, including head elevation(16), subglottic suctioning(13), continuous cuff pressure monitoring and oral care(17). A biofilm could form inside the lumen of the tube and drop off into the lung(13–15). Therefore, the circuit used to be changed routinely to ensure that the circuit was clean without any scientific evidence that this was necessary or effective.

Recent studies showed that a higher frequency of circuit change is associated with a higher risk of VAP(18). This can be explained as the IMV circuit being a closed system; the more times it is disconnected, the greater the chance of introducing external microorganisms(13, 19). Therefore, the US Centers for Disease Control and Prevention (CDC) and the Health care Infection Control Practices Advisory Committee no longer suggest regular changes in circuits(20). Instead, the circuit only needs to be replaced when the equipment is visibly soiled or malfunctioning(20).

For nonintubated patients, the causes of HAP are totally different. The main pathogenesis is aspiration and inhalation of microbial aerosols(10). Unlike IMV, the NPPV circuit is an open system that is often disconnected, so it can be contaminated much more easily. The pathogen counts were found to be significantly different at the two ends of the circuit. Namely, the number of pathogens in the mask (patient end) was higher than that in the tube near the ventilator end(21, 22). It can be assumed that the pathogens possibly migrate into the circuit from the mask side, which is open to the environment. Theoretically, this would increase the chance of the patients inhaling the microbial aerosol generated by this high-flow oxygen therapy.

From another aspect, the patient’s airway clearance ability exists because they are not sedated and the function of the cilia is not disturbed. Their upper respiratory function is maintained, and the natural protective barrier of the respiratory tract is not destroyed. From the perspective of “noninvasive”, microorganisms in the lumen of the tube are less likely to enter the lower respiratory tract. These thoughts invoke two conflicting assumptions: Will the microorganisms in the tube be the direct cause of HAP because the NPPV circuit is an open system and high flow gas could generate more microbial aerosol? Or, will patients who have circuits changed only when clinically indicated have equivalent rates of HAPs with patients whose circuits are routinely changed every 7 days?
Different answers were found in past studies. Zhong's study showed that there were more circuits contaminated by common HAP pathogens on the 7th day than on the 3rd day, but the patients who developed HAP at the two different time points were not significantly different (21). Unfortunately, the diagnostic criteria for HAP are unclear in this report. Ding's study (22) showed that colonies in the same site in the NPPV circuit were not significantly different every two days, but the observations did not continue after the 7th day because circuits were not disposable in their study. Therefore, they still suggest an every 7-day change of circuit without solid evidence. Conversely, Sanner (23) reported that long-term home NPPV patients who cleaned their devices regularly and adequately experienced significantly lower rates of upper airway infections (13.3% vs. 52.4%) during a six-month treatment period. This indicates that circuits may be a contributor to pneumonia in NPPV patients. However, the circuit material has changed greatly since then and has become nonreusable. In fact, for many patients, especially patients with chronic respiratory disease, such as chronic obstructive disease (COPD), the length of NPPV treatment is often 7 days or more. Moreover, patients with long-term conditions usually have impaired immune ability. The maximum duration of safe use of a circuit is an issue of concern in clinical practice (18) and should be addressed.

The literature illustrated above provides limited evidence for focusing on the most suitable interval for changing circuits. To our knowledge, it remains unknown how long one circuit can be safely maintained. HAP in noninvasively ventilated patients is not as low as sometimes supposed, with a rate ranging from 0 to 41% (2, 5) in large populations from various healthcare settings. Therefore, HAP during NPPV requires scientific prevention strategies. HAP differs from VAP in populations and causes. The evidence from IMV cannot be directly applied to NPPV. We are planning a study to explore how long the circuit can be used safely with an adequate number of participants and a robust design.

Objectives

The primary aim of this trial is to compare the occurrence of HAP in the routine NPPV circuit change group with the clinically indicated change group. Secondary aims include understanding the growth curve of microorganism colonies in the NPPV circuit; determining the maximum duration of safe use of a circuit; establishing whether clinically indicated circuit changes could lead to a reduction in direct costs; and identifying risk factors associated with HAP in patients receiving NPPV therapy.

Methods And Analysis

Study design

This is a nonblinded, prospective, randomized trial comparing routine and clinically indicated changes in circuits for the prevention of HAP in patients who receive NPPV therapy. Ethical approval was obtained from the local ethics committee in the leading hospital (issue NO. 2022 review (183)).

Patient involvement
Study setting

Patients admitted to the pulmonary disease departments of two tertiary hospitals in Chengdu, China, will be recruited for this study for convenience sampling. There are two pulmonary disease nursing wards with 84 beds in each ward in WC Hospital and 54 beds in the pulmonary disease department in SJNF Hospital. WC Hospital is a national teaching hospital located in western China that serves populations from many western and southwestern provinces. SJNF Hospital is a branch of WC Hospital that mainly serves the local population in Chengdu City while receiving triaged patients from WC Hospital. As a central hospital in southwestern China, each respiratory department receives approximately 260 patients on average every month. Among these patients, over 60% are critically ill patients with a high utilization of NPPV. This can help ensure adequate participant involvement to reach the target sample size.

Inclusion and Exclusion Criteria

In each participating hospital, patients with different kinds of respiratory diseases who require NPPV therapy will be screened for eligibility by the research nurses (WLL, WY&ZYH). The recruitment will be from May 2022 and end in May 2023 because the moisture and temperature differ among the four seasons, which could influence the factors for microorganism growth. Inclusion criteria: (1) aged 18 years or older; (2) receiving NPPV therapy at least 4 hrs per day; (3) estimated NPPV therapy longer than 48 hrs; and (4) voluntary participation. Exclusion criteria: (1) Known contagious respiratory disease; (2) NPPV has already been used in other departments or hospitals for the same course of treatment before transferring to the participating pulmonary disease departments; (3) Known hospital-acquired infection before NPPV onset; (4) Immunodeficiency (including but not limited to malignant tumors, patients with radiotherapy and chemotherapy, acquired immunodeficiency syndrome, taking immunosuppressants); (5) Hypoalbuminemia; (6) Dysphagia; (7) History of gastroesophageal reflux disease; (8) History of aspiration; (9) Obesity (BMI 28 kg/m²); (10) History of head and neck, chest or upper abdominal surgery in the past 3 months; (11) ICU history during this admission. All patients (or their legal surrogates if the patient is incapable of decision-making) will be fully informed of the aim and content of this study by both an oral explanation and a written information sheet. Written informed consent will be obtained from the patients or their surrogates before enrollment.

Sample size estimation

This is a noninferiority randomized control trial. Based on data from a small pilot study conducted domestically, the rate of HAPs in adult patients with NPPV was approximately 23.5% (21). The sample size was calculated to test equivalence at 23.6% (δ = 0.1) HAPs between two groups with 5% significance and more than 80% power. This means a total number of 309 patients, plus more than 10% of patients to allow for possible withdrawal. As a result, 340 patients will be included in this study.

Randomization and masking

Patients will be randomly assigned to one of the two groups stratified by hospital (WC Hospital: SJNF Hospital = 3:2) with a randomization ratio of 1:1. The project statistician (not involved in the clinical
intervention) will use SPSS software (version 24.0) to generate random numbers. The research nurses who are responsible for patient enrollment will not have access to the patient allocation and assignment. Each patient will be given a concealed envelope for random allocation at the point of each patient’s study entry. After allocation, the participants and the clinical nurses could not be masked because they would naturally know the length of the circuit dwelling time. The investigators will not be masked because they will allocate patients to different groups and monitor the integrity of the intervention daily. However, the patient’s responsible physician and laboratory staff will be masked for diagnosing HAP and for rating all microbiological endpoints, respectively.

**Procedures**

Patients in the intervention group will have their circuit changed or disposed only for clinical reasons, including a broken circuit, completion of NPPV therapy, visible contamination or indications of a suspected infection. Patients in the control group will have their circuit changed every 7 days unless it is clinically impossible (e.g., the circuit is broken or contaminated before Day 7). None of the researchers can be involved in making decisions to change the circuit, but the clinical nurses will do so. All of the included patients will use a Type V60 noninvasive ventilator (Respirronics California, LLC). The whole circuit consists of a mask (Emedical®, Excellentcare Medical Ltd. Huizhou, China), tube (Emedical®, Excellentcare Medical Ltd. Huizhou, China) and continuous-feed humidifier (Type MR290, Fisher&Paykel, Auckland, New Zealand). The type and size of the masks are not unique but vary by the size and shape of the patient’s face, arterial blood gas test, patient tolerance and physician choice.

According to the hospital protocol for NPPV treatment, sterilized water will be used for humidifying and it will be replaced every 24 hrs in both groups. Additionally, a filter (Type Hygrobac S, Covidien LLC, USA) will be connected between the gas outlet of the ventilator and tube with weekly replacement or when air resistance obviously occurs. Other HAP prevention methods(16) will also be routinely followed in each group (medical worker’s hand hygiene(24), head-up position(25), oral care(26) or tooth brushing(24) at least 2 times per day, gargling after each meal, airway clearance guidance(24), and early motivation). Filters inside the ventilators will be changed routinely according to the ventilator manual made by the company.

The research nurses (FM, ZJ & ZYH) will use a checklist to check adherence to the intervention protocol and HAP prevention protocol daily by observing the patients’ and nurses’ behaviors and by asking the patients about their health-relevant knowledge. There is also a part-time hospital infection control nurse working in every nursing ward as required by the hospital. This person daily monitors staff compliance with the hospital infection control protocol. The treatment of the primary disease will be performed by the clinical physicians per routine care. When confirmed HAP occurs, the interventions will be discontinued in both groups, and the patients will return to routine management of NPPV therapy. We will not modify the participant’s allocation since the individual’s recruitment. If the participant asks to withdraw from the trial, we will ask for the reasons, record it and respect the patient’s autonomy, but they will be treated as a dropped-out participant in the analysis. Figure 1 shows a flowchart of the study procedures.
The diagnosis of HAP

The diagnosis of HAP will be based on the criteria for VAP in MV of the 2018 Guidelines for the Diagnosis and Management for HAP/VAP in Chinese adults issued by the infectious disease group of the Chinese Thoracic Society (CTS), Chinese Medical Association(10). The clinical diagnostic criteria included (1) 48 hrs or more after ventilation or weaning from ventilation within 48 hrs; (2) radiology: new or progressive and persistent infiltrates, consolidation or ground glass shadow; and (3) in addition to radiology, at least two of the following signs and symptoms: fever over 38°C with no other recognized cause, leukocyte count over 10x10^9/L or less than 4 x10^9/L, and new onset of purulent sputum. At the same time, at least one of the following pathogenic diagnosis criteria was used: (1) lower respiratory tract aspirate showing > 25 neutrophils and < 10 epithelial cells per low-power field; (2) positive culture from sputum, endotracheal aspirate, BAL, lung tissue, PSB or other aseptic humoral; (3) positive lung histopathology, cytopathology or direct microscopic examination for fungus and related evidence of lung tissue damage; and (4) positive diagnostic test for virus in the respiratory secretions.

The investigators will not be involved in assessing a suspected HAP, but the clinical physicians will diagnose HAP according to the CTS criteria and order the HAP tests. The standard bundle of HAP tests included blood culture, complete blood count, respiratory aspirate microscopy and culture, and chest X-ray. On the same day, a microbiological sample swabbed from 4 sites in the tube will be cultured to identify if it is the same as that identified from the sputum or respiratory secretions. This microbial sampling will be carried out by the three trained hospital infection control nurses who are not involved in the study in the two hospitals. The 4 sites are 5 cm deep from the start of the tube, condensate water cup, humidifier and masks (Fig. 2). The sampling process will follow the medical equipment surface sampling method recommended by the Technical Standard for Disinfection of Medical and Health Structures in Technical Standard for Disinfection by the Ministry of Health, China(27).

Data Collection

Patients’ baseline data will be collected within 24 hrs after entering the study. A paper-based case report file will be used for each patient information record. The data collected have been selected based on a literature(5, 15, 28) review and clinical relevance, including demographic data (age, sex, body weight and patient source), medical history (underlying disease, reflux and aspiration in this hospitalization, indication for NPPV therapy, Charlson Comorbidity Index and Acute Physiology and Chronic Health Evaluation II score) and clinical management (ventilation modality, actual ventilation hours per day, antibiotics usage, other catheters such as feeding tube, H2 blocker usage, nebulizer inhalation therapy, open suction system usage, other catheters). The samples from the same sites in the tube will also be taken for culture lump-sum analysis every 48 hrs (48 hrs, 96 hrs...48 N hrs, N = 1,2,3,...n) and at the end of circuit use for each circuit in both groups. Table 1 shows the schedule of enrollment, interventions and assessment.

Clinical outcomes
The HAP rate will be the primary outcome compared between the two groups. The primary outcome will be follow-up until 48 hrs after weaning from NPPV, transfer to another department, discharge or death, whichever is soonest. The length of hospital stay, length of each circuit duration, NPPV treatment days, clinical prognosis (intubation and mortality) and direct cost of circuits and antibiotics will be analyzed as secondary outcomes. Secondary outcomes will be followed as scheduled (see Table 2).

**Statistical analyses**

SPSS software (V. 24.0, SPSS, Chicago) will be used for conducting the statistical analysis. Data will be expressed as the mean (SD) for continuous variables and counts (percentages) for categorical variables. Continuous variables will be compared by independent Student’s t test or the Mann–Whitney U test and Chi-square test or Fisher’s exact test for categorical variables. ORs and relevant 95% CIs will be adopted for assessing associations between potential risk factors and outcomes. Multivariate logistic regression will be used to investigate the effects of potential risk factors on the development of HAP in patients receiving NPPV therapy. A P value less than .05 will be considered statistically significant. A 2-sided design will be used to test equivalence between groups with more than 80% power.

**Provisional statistics analysis plan**

The planned analyses are as follows:

A. Clinical features, management and outcomes of the patients

All patients will be included in the analysis. Comparisons will be performed between the patients in the intervention and control groups for their demographics, medical history, clinical management and outcomes.

B. HAP and its potential cause

HAP is the primary outcome in this trial. The HAP rate will be compared as HAPs per patient and HAPs per 1000 ventilation days to see if it is significantly different between the two groups. According to the analysis, the circuit change time interval can be defined as a cause of HAP or not. Per-protocol analysis will exclude patients who are noninvasively ventilated for less than 48 hrs and participants who require withdrawal from this trial. Intent-to-treat analysis will include all participants according to the initial randomized allocation. Death will be treated as a competing event; therefore, the cause-specific cumulative incidence will be counted and compared between the groups using a Fine-Gray regression model.

C. Risk factors associated with HAP in patients receiving NPPV therapy.

The patients who develop HAP will be compared with patients without HAP. Multivariate analysis will be performed to explore factors that independently predict the development of HAP.

D. Economic considerations
Direct costs of circuits will be compared between the groups, including the costs for labor and equipment supplies. We estimate that the total cost per circuit change is 800 CNY (115.6 USD), which includes a tube, a humidifier and a mask. The nursing labor cost spent on changing circuits will not be included. The cost of antibiotics will also be compared between the groups. These data will be abstracted from the patient’s hospital bill upon discharge.

E. Microbial analysis in the study groups

Pathogenic microorganisms will be isolated from the tracheal aspirates and circuits from the patients who develop HAP on the same day to see if they are from the same source. The microbial colony count from all circuits will be compared at different time cutoffs (every 2 days) and for different sites (mask, humidifier, 5 cm deeper from the start of the tube and condensate water cup). Growth curves of the microorganisms will be drawn to show their growth patterns in the circuits.

Data management

Relevant data will be collected onto a CRF. After the follow-up is finished, the CRFs will be deidentified by removing patient identifiers. Two research nurses will be trained to double-enter all clinical data from the CRFs and from the laboratory tests into ResMan. The third investigator will check the data accuracy if data inconsistency occurs, and this investigator will trace it back to the original form.

Researchers from the central management team and relevant regulatory authorities will have access to the web-based databases during the trial. After data analysis and article publication, individual patient data without identifiers will be available to the public via ResMan (http://www.medresman.org/), for which consent will be sought from each participant at the very beginning of the study. CRFs in the other hospital will be sent in person to the central office and together with the others stored in a locker in the office in the leading hospital for 5 years upon completion of the study (last patient follow-up finished); thereafter, digital copies will be retained for 10 years. Participants’ names or other identifiers will not appear in any database, publications or reports.

Data and safety monitoring

A formal data monitoring committee (DMC) will not be included in this trial for budget reasons. A statistician who is not involved in the clinical phase will analyze the data at a priori defined intervals (n = 100, n = 200) and will decide to continue or terminate the trial. One planned stopping rule is a greater than 2:1 ratio in either group for HAPs. Group meetings will be held monthly to assess the adherence of study administration to the protocol and the progress of study conduction.

The research team consists of the principle investigator (WLL) in the leading hospital and the main investigators in the two hospitals (ZXL, WY, WF, LJ, WMJ, ZYH, WWX, HY, ZJ, FM, ZX). Their detailed working allocations are explained as follows: The PI will be responsible for monitoring the conduct of the study to ensure compliance with Good Clinical Practice guidelines and the study protocol as well as organizing group and training meetings. The PI also has the responsibility for reporting adverse events.
The main investigators will be responsible for day-to-day management of the study. It includes patient recruitment (WY, WLL&ZYH) and assignment (WF, ZXL), daily checks of protocol adherence (FM, ZJ&ZYH), staff training (LJ, WMJ, WY, ZYH, HY), data collection and checking (ZXL, WWX, WY), data analysis (ZX, ZXL, WWX), and preparing reports and publications (ZXL, WY, ZJ, WLL, WWX). The ethics committee will perform continuous audits of the study independently from the investigators and the sponsor of this research.

Adverse events are commonly seen but are not severe in patients receiving noninvasive ventilation, including but not limited to pressure ulcers, conjunctivitis and bloating. Events that will be reported to ethics committees are (1) all-cause serious adverse events during hospitalization, (2) all serious adverse events judged possibly to be related to the dwelling time of the circuit and (3) all deaths and palliative discharges. The reporting process will follow good clinical practices.

Discussion

The aim of this study is to explore the relationship between the time interval of circuit change and HAP occurrence. We also hope to identify the best time cutoff and most cost-effective circuit change strategy for NPPV management. To the best of our knowledge, this is a pioneer study with an adequate sample size, strict diagnostic criteria and robust design to evaluate the influences of prolonged dwelling time of noninvasive ventilator circuits on HAP occurrence. It also evaluates the clinically relevant outcomes concerning antibiotic usage and equipment cost-effectiveness.

Pathogen colonization in circuits could be a source of hospital-acquired infection for patients on NPPV therapy. Unlike an invasive ventilation circuit, which is a closed loop, a noninvasive ventilation circuit is an open system that is often disconnected, making it much easier to be contaminated by pathogens within the hospital environment. When the ventilator generates high-velocity gas flow, a biofilm could blow off from the lumen of the tube, and the microbial aerosol could disperse further(29). However, there is no evidence suggesting that after the 7th day, the accumulation of microorganisms has peaked. In contrast, one small sample size study showed that the microorganism colony count in the circuit does not change during the first seven days, but the growth trend after that time point was not reported(21).

Bacterial growth has four phases: lag, log, stationary and decline. What if after seven days the growth decreases; in that case, what is the reason for changing the circuit every seven days? To make the propagation pattern clear, we will monitor the microorganism count in the circuit every two days to complete the growth curve of the microorganisms in the ventilator circuit. Thus, we could analyze the relationships among circuit dwelling time, microorganism growth time and HAP occurrence. Moreover, the suspicious influencing factors on HAP are complex, including growth of the microorganisms, ventilation modality and participants’ factors. We randomly assigned the participants to the two groups to determine whether the single factor of dwelling time could be a cause of HAP in patients receiving NPPV.

Limitations
First, due to budget limitations, we will not carry out pathogenic detection for all circuits. Instead, when suspicious or confirmed HAP occurs, a sample from the circuit will be taken for pathogenic detection. Aspirates from the airway will be taken and cultured at the same time to test whether the pathogens are from the same source. Second, the inclusion criteria are very strict, and only patients in the respiratory department will be included, limiting its application to a larger population. This is because there are no adequate former studies on this topic. Considering that the primary endpoint of the trial is HAP, for the purpose of safety, we excluded all vulnerable populations and have started on a small scale. However, this pilot study is clinically vital and meaningful: if the results prove that circuit dwelling time is not relevant to HAP, the population can be enlarged in future studies. As NPPV is widely used in hospitals and other healthcare settings, if supported by the evidence, the proposed circuit change strategy could be a potential cost-effective method, saving the healthcare system a considerable amount.

**Ethics And Dissemination**

Ethical approval was obtained from the local ethics committee in the leading hospital (Issue NO. 2022 review(183)). This trial has also been registered in the Chinese Clinical Trial Registry (NO. ChiCTR2200059607. Registered in April 2022. Protocol version: 2.0; issue date May 4, 2022). Participant enrollment cannot be started until the written permit of ethical approval is obtained and sent to the leading hospital. All participants will be fully informed of the study, and written consent forms will be obtained before their entry into this research. If any modification of the study design is made, the PI is responsible for reporting it to the ethics committee for approval of the change implementation. The findings will be presented in relevant peer-reviewed journals in infection control and respiratory medicine to communicate the trial results with the participants, healthcare professionals and other relevant groups. As the participants will not be familiar with peer-reviewed medical journals, the published article will be sent to any participant who specifically asks for it.

**Trial Status**

This study is in the process of patient recruitment and clinical intervention. Participant recruitment began on May 5th, 2022, and recruitment was planned to be completed on May 5th, 2023. However, due to the pandemic and temporary lockdown in the authors’ city in September, recruitment is expected to be prolonged.

**Abbreviations**


**Declarations**
Declaration of interest:

None

Ethics approval and consent to participate

Ethical approval was obtained in West China Hospital, Sichuan University (Ref NO. 2022 review(183)). This trial is also registered in Chinese Clinical Trial Registry (NO. ChiCTR2200059607) in April, 2022. Protocol version: 2.0; issue date May 4, 2022. All patients (or their legal surrogates if the patient is incapable in decision making) will be fully informed with the aim and content of this study by both oral explanation and written information sheet. A written inform consent will be obtained from the patients or their surrogates before enrollment by trained research members following consent procedures. All participants have autonomy to withdraw at any process of the study.

Consent to publication

Not applicable

Availability of data and materials

After data analysis and article publication, individual patient data without identifiers will be open for public via ResMan (http://www.medresman.org/), for which the consent will be sought from each participant at the very beginning of the study. The biology samples will not be stored for further use after laboratory test, but will be bio-safely disposed following hospital protocol.

Competing interests

All the authors declaim no conflict of interests

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Authors’ contributions
WY and WLL conceived the study; involved in designing study and applying for ethic permission. WLL was also responsible for funding acquisition. WY and WLL development the research protocol. ZXL and ZJ were involved in the manuscript drafting and editing. LJ provided infection control expertise for the study design. LJ and WMJ will supervise and perform microbiological analyses. WY and WLL reviewed the manuscript. WF, ZYH, WWX, HY, FM and ZX are members of this trial who are going to conduct and manage the study. All authors read and approved the final manuscript.

Acknowledgement

None.

References


Tables

Table 1 and 2 are available in Supplementary Files section.

Figures
Figure 1: Flowchart of study procedures
NPPV: noninvasive positive pressure ventilation; VC: ventilator circuit

Figure 1
See image above for figure legend
①: 5cm deep from the start of the tube
②: humidifier
③: condensate water cup
④: mask

Figure 2. Illustration of the 4 microbiological sampling sites

Figure 2

See image above for figure legend

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- T1scheduleofenrolmentinterventionsandassessment.pdf
- T2followupperiodsforallstudyponits.pdf
- SPIRITChecklist.doc
- Appendixlinformedconsent.pdf