PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A parallel-group, randomized, controlled, non-inferiority trial of high-flow nasal cannula versus non-invasive ventilation for emergency patients with acute cardiogenic pulmonary edema: study protocol
AUTHORS	Ruangsomboon, Onlak; Praphruetkit, Nattakarn; Monsomboon, Apichaya

VERSION 1 – REVIEW

REVIEWER	Ilhan Uz Ege University Faculty of Medicine
REVIEW RETURNED	19-Jun-2021

GENERAL COMMENTS	I congratulate you for preparing this protocol so well.

REVIEWER	Hugo de Carvalho Universite de Nantes - Faculte de Medicine, Emergency Medicine
REVIEW RETURNED	24-Jun-2021

GENERAL COMMENTS	Thank you for the opportunity to review bmj-2021-052761. This is a study protocol which aims to assess the non-inferiority of high-flow nasal cannula versus non-invasive positive pressure ventilation for emergency patients with acute cardiogenic pulmonary edema. To my knowledge this is the first study comparing HFNC to NIPPV in ACPE. There is some concern about the rational and the design of the study. 1/ Almost half of patients with ACPE are hypercapnic. Positive pressure through NIPPV is a quick and effective way to treat hypercapnia. HFNC is known to produce a mild positive pressure but to my knowledge, no work support is capacity to treat hypercapnia. The authors should address this issue in their introduction. A subgroup analysis should be performed to investigate if the treatment is modified by different initial severity of hypercapnia. 2/ Requiring an initial chest radiograph before inclusion may exclude more severe patients needing immediate treatment, with the highest risk of needing endotracheal intubation during the 72hours following inclusion. Moreover, authors states that the duration time from eligibility assessment and study initiation could go up to 60 minutes. Again this time frame may exclude severe patients. This could lead to a significant selection bias. 2/ Patients presenting at the Emergency department with ACPE needing NIPPV often present with respiratory distress signs. Informed consent in such situation may not be obtained. If local laws allow such thing, authors should ask for relatives' consent or have an emergency inclusion protocol with delayed consent by the patient. If local regulation does not allow this kind of inclusion, it should be stated in the manuscript.

	3/In “exclusion criteria”, authors states that abdominal dyssynchrony is an exclusion criteria. It is unclear why this sign of respiratory distress alone should justify immediate endotracheal intubation. In the same sentence, they write that “SpO2 < 90% despite oxygen supplement at FiO2 = 1.0” is an exclusion criterion despite this FiO2 being only available through NIPPV, endotracheal intubation or HFNC. 4/ In table 1: Arterial blood gas are only performed at one hour when the total time of NIPPV or HFNC use is 4 hours. Respiratory rate, blood pressure and other parameters are only monitored during the 24 hours despite the primary objective being the intubation rate during the first 72 hours. Medication given to the patients in each group should be monitored. 5/ It is unclear why the lung ultrasound assessment should not exceed 3 minutes.

REVIEWER	Jie Li Rush University, Cardiopulmonary Sciences, Division of Respiratory Care
REVIEW RETURNED	01-Jan-2022

GENERAL COMMENTS	Thanks for inviting me to review this protocol of a RCT to compare HFNC vs NIPPV to treat patients with acute cardiogenic pulmonary edema. I’d like to congratulate the authors for designing the first RCT on this topic. My comments are shown below: Major: 1. In figure 1: study procedures: between the “primary and secondary outcomes” and “primary analyses”, there is a box of “excluded- diagnosis not ACPE”: do you mean you would exclude the patients at the phase of data analysis because patients are not diagnosed as ACPE? your inclusion criteria is ACPE, how can you exclude the patients with non-ACPE? More importantly, you already enroll them and provide assigned treatment until the ending point, how can you exclude the patients at such late phase? Authors please clarify. 2. Outcomes: In figure 1: “failure: ETT or crossover”: do you count endotracheal intubation or crossover as treatment failure? however, in the abstract, you said “treatment failure rate (a composite of intolerance, intubation, and mortality).” please clarify. Likewise, at the end of introduction section, you stated “the primary aim of this randomized study is to determine if the use of HFNC results in a non-inferior intubation rate compared with NIPPV in ED patients with ACPE. The key secondary aims are to evaluate the effects of HFNC compared to NIPPV on the rate of intolerance, intubation, and mortality.”: do you mean the “key secondary aims” as “treatment failure rate (a composite of intolerance, intubation, and mortality)” or individual outcome? if you mean the rate of intolerance, the intubation rate, and mortality individually, please remove the intubation rate, as it is already listed as the primary outcome. Authors please present the outcomes consistently. 3. Cross-over: To me, the major concern for this study design is the cross-over, how can the authors control the cross-over rate and analyze the data with cross-over patients should be presented in the method section. 4. Discussion: the discussion section is too short, authors please expand. For example, the clinical implication of this study. Minor: 1. “arterial pressure of oxygen (PaO2)/FiO2< 300 or SpO2/FiO2<

	240": according to the equation (S/F = 64 + 0.84 x (P/F) by Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest. 2007;132:410-417. When PF is 300, SF is 315, therefore SF <240 is not comparable to PF<300. Secondly, what's the oxygen device when the PF or SF is decided? As the oxygen device plays a crucial role in oxygenation and the accuracy of FIO2, the authors need to clarify what type of oxygen device would be used at study screen. 2. Authors will use ROX index and lung ultrasound scores to predict the intolerance rate, this is the first time I have ever seen to use ROX index and lung ultrasound scores to predict the intolerance for HFNC or NIV, authors please explain the rationale. 3. For NIPPV group, what oxygen device will be used in the break of NIPPV sessions? Will HFNC be allowed to use in-between NIPPV?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ilhan Uz, Ege University Faculty of Medicine
Comments to the Author:
I congratulate you for preparing this protocol so well.

Reviewer: 2
Dr. Hugo de Carvalho, Universite de Nantes - Faculte de Medicine
Comments to the Author:
Thank you for the opportunity to review bmj-2021-052761. This is a study protocol which aims to assess the non-inferiority of high-flow nasal cannula versus non-invasive positive pressure ventilation for emergency patients with acute cardiogenic pulmonary edema. To my knowledge this is the first study comparing HFNC to NIPPV in ACPE. There is some concern about the rational and the design of the study.

1/ Almost half of patients with ACPE are hypercapnic. Positive pressure through NIPPV is a quick and effective way to treat hypercapnia. HFNC is known to produce a mild positive pressure but to my knowledge, no work support is capacity to treat hypercapnia. The authors should address this issue in their introduction. A subgroup analysis should be performed to investigate if the treatment is modified by different initial severity of hypercapnia.

We appreciate the reviewer's thoughtful comment. A recent meta-analysis assessing the efficacy of HFNC compared to NIPPV involving 621 hypercapnic patients from 6 RCTs and 2 cohort studies found that HFNC was non-inferior to NIPPV with respect to intubation rate (doi: 10.1155/2020/7406457) Nonetheless, a subgroup analysis that the reviewer kindly suggested will increase the value of the evidence found in the present study. Therefore, we will conduct the subgroup analysis as suggested. We have revised the statistical analysis section accordingly, stating that "Planned exploratory subgroup analyses will be performed to investigate if the treatment effect is modified by different initial severity of hypoxemia and hypercapnia."

2/ Requiring an initial chest radiograph before inclusion may exclude more severe patients needing immediate treatment, with the highest risk of needing endotracheal intubation during the 72hours following inclusion. Moreover, authors states that the duration time from eligibility assessment and study initiation could go up to 60 minutes. Again this time frame may exclude severe patients. This could lead to a significant selection bias.

Our ED is equipped with a portable X-ray machine and a radiology technician who can perform X-ray 24/7 and the film can be read at the machine right after it is performed. The process from ordering an X-ray to reading the film usually takes less than 5-10 minutes. In general (non-research) cases in which we think that non-invasive respiratory support measures are to be required, we can complete all the X-ray process while preparing the equipment. In this case (research), we think that the process of X-ray is equivalent to the time taken to prepare and heat HFNC and NIPPV equipment in case the patients are eligible; therefore, we think it is best to confirm the diagnosis prior to recruiting patients. As for the duration from eligibility assessment to study initiation of 60 minutes, we do agree with the

reviewer that it may be too long, so we decide to revise it to 20 minutes maximum, allowing time for machine preparation and at least verbal consent.

2/ Patients presenting at the Emergency department with ACPE needing NIPPV often present with respiratory distress signs. Informed consent in such situation may not be obtained. If local laws allow such thing, authors should ask for relatives' consent or have an emergency inclusion protocol with delayed consent by the patient. If local regulation does not allow this kind of inclusion, it should be stated in the manuscript.

Our institutional review board allows us to obtain only verbal consent from the patients or their legal representatives (next of kin) prior to inclusion. Written consent can be sought after later when the patients' symptoms alleviate, and they are clinically stable. We have revised the ethics section accordingly, stating that "Verbal consent from either the participants or their legal representatives will be initially acquired before trial inclusion with a written form obtained from the participants or their next of kin later when their' symptoms are stabilized."

3/In "exclusion criteria", authors states that abdominal dyssynchrony is an exclusion criteria. It is unclear why this sign of respiratory distress alone should justify immediate endotracheal intubation. In the same sentence, they write that "SpO2 < 90% despite oxygen supplement at FiO2 = 1.0" is an exclusion criterion despite this FiO2 being only available through NIPPV, endotracheal intubation or HFNC.

The need for immediate endotracheal intubation without attempting non-invasive respiratory measures are in fact clinically subjective by each physician. With the reviewer's comment, the authors have discussed and agreed on a revised criteria that all participating clinicians also accept. We have revised the exclusion criteria for needing immediate intubation upon eligibility assessment to "Respiratory failure needing immediate endotracheal intubation, defined as RR > 35 breaths/min, SpO_2 < 90% despite oxygen supplement at the highest level of FiO_2 possible via oxygen mask with reservoir bag, and signs of severely increased work of breathing as determined by the attending physicians"

4/ In table 1: Arterial blood gas are only performed at one hour when the total time of NIPPV or HFNC use is 4 hours.
Respiratory rate, blood pressure and other parameters are only monitored during the 24 hours despite the primary objective being the intubation rate during the first 72 hours. Medication given to the patients in each group should be monitored.
Arterial gas: we will record arterial gas results for the trial purpose at one hour. It is true that more arterial gas should be performed (at least in some patients), but we will leave the decision at the discretion of the attending physicians as to when and how many times they will measure as this decision is based on each patient's clinical improvement. Also, weaning of these non-invasive airway measures can be done with clinical assessment alone without gas results in non-hypercapnic cases. And assessing patients' gas results too often or unnecessarily for trial purposes may be considered invasive and unethical. Therefore, we decided to keep the protocol assessment of arterial gas to only one time.

As for other physiologic parameters, they are monitored as per the standard of the hospital's inpatient department. For the trial purpose, we plan to only record them daily after 24 hours has passed, as has been revised in the methods section.

5/ It is unclear why the lung ultrasound assessment should not exceed 3 minutes.

The process of lung ultrasound assessment can be a burden to the participants, especially when they are in respiratory distress. Our emergency ultrasound specialists thus recommend that the process (considering the expertise of the scanners and the number of scans required) should not exceed 3 minutes. We have included the reason for better clarification, stating that "The total duration for lung ultrasound assessment (excluding score calculation) at each time point shall not exceed 3 minutes to minimize the participants' possible distress and burden from the assessment process."

Reviewer: 3

Dr. Jie Li, Rush University
Comments to the Author:
Thanks for inviting me to review this protocol of a RCT to compare HFNC vs NIPPV to treat patients with acute cardiogenic pulmonary edema. I'd like to congratulate the authors for designing the first RCT on this topic. My comments are shown below:

Major:
1. In figure 1: study procedures: between the "primary and secondary outcomes" and "primary analyses", there is a box of "excluded- diagnosis not ACPE": do you mean you would exclude the patients at the phase of data analysis because patients are not diagnosed as ACPE? your inclusion criteria is ACPE, how can you exclude the patients with non-ACPE? More importantly, you already enroll them and provide assigned treatment until the ending point, how can you exclude the patients at such late phase? Authors please clarify.

As stated in the analysis section, we will perform a modified intention-to-treat (mITT) analysis as the primary analysis. This mITT analysis will include all patients randomized excluding those later deemed to not have ACPE by the trial adjudication committee. While the full ITT analysis will also be performed as a sensitivity analysis including all randomized patients. This decision is decided upon because ACPE is an acute condition usually diagnosed clinically in the ED. Nonetheless, many patients who are initially diagnosed as ACPE are later reviewed to have other diseases, such as airway diseases. Including them in the primary analysis will thus produce noise in the data because they are a population without the condition of interest. Therefore, we decide to perform mITT as the primary analysis. Patients who are later excluded due to being adjudicated otherwise will be included in the full ITT analysis as has been stated in the analysis section (Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. BMJ. 2010;340:c2697).

2. Outcomes: In figure 1: "failure: ETT or crossover": do you count endotracheal intubation or crossover as treatment failure? however, in the abstract, you said "treatment failure rate (a composite of intolerance, intubation, and mortality)." please clarify. Likewise, at the end of introduction section, you stated "the primary aim of this randomized study is to determine if the use of HFNC results in a non-inferior intubation rate compared with NIPPV in ED patients with ACPE. The key secondary aims are to evaluate the effects of HFNC compared to NIPPV on the rate of intolerance, intubation, and mortality.": do you mean the "key secondary aims" as "treatment failure rate (a composite of intolerance, intubation, and mortality)" or individual outcome? if you mean the rate of intolerance, the intubation rate, and mortality individually, please remove the intubation rate, as it is already listed as the primary outcome. Authors please present the outcomes consistently.

The primary outcome is intubation. The secondary outcomes are intolerance rate, mortality rate, and failure rate (composite of intubation, intolerance, and mortality). We apologize for the clerical error and have revised all the sections (abstract, methods, and figure) accordingly.

3. Cross-over: To me, the major concern for this study design is the cross-over, how can the authors control the cross-over rate and analyze the data with cross-over patients should be presented in the method section.

We acknowledged the reviewer's concerns as we also agree that crossover may be an issue with the trial results (especially the primary outcome). Nonetheless, crossover to the other arm due to intolerance is one of the outcome that we would like to measure. In trying to minimize crossover from other reasons than intolerance, we specified switching criteria to avoid such circumstances. Also, we have educated and advised our research personnel, participating physicians and nurses against such contamination and emphasized the purpose of the trial and the importance of following the protocol as stated in the 'protocol consistency' sub-heading. For statistical analyses, we will use statistical methods such as casual estimation techniques to control for crossover. However, under the discussion with our statistician, we deem that specifying in the protocol of the exact statistical method that we will use to manage crossover may not be appropriate as the most appropriate choice may also depend on the characteristics of the data. Therefore, we have added a statement in the analysis section as follow; "Analytical methods to adjust for contamination will also be employed as appropriate."

4. Discussion: the discussion section is too short, authors please expand. For example, the clinical implication of this study.

We appreciate your insightful comment. We have added a discussion section in combination with the previous strengths and limitations section in the revised version of the protocol.

Minor:
1. "arterial pressure of oxygen (PaO2)/FiO2< 300 or SpO2/FiO2< 240": according to the equation (S/F = 64 + 0.84 x (P/F) by Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest. 2007;132:410-417. When PF is 300, SF is 315, therefore SF <240 is not comparable to PF<300. Secondly, what's the oxygen device when the PF or SF is decided? As the oxygen device plays a crucial role in oxygenation and the accuracy of FIO2, the authors need to clarify what type of oxygen device would be used at study screen.

We apologize for this error. We initially based our calculation of SF ratio from PF ratio on a study in pediatric patients by Bilan, et al. (doi: 10.15171/jcvtr.2014.06) which has a different formula than the one from Rice, et al. We revised the criteria accordingly and, again, sincerely apologize for the error.

The oxygen supplement device upon initial assessment in general practice at our ED is standard nasal cannula or oxygen bag with reservoir mask. FiO2 is estimated from L/min of oxygen delivered through each device.
We have revised the criteria to "Pulse oximetry (SpO_2) < 92% when breathing at room air or arterial pressure of oxygen (PaO_2)/FiO_2< 300 or SpO_2/FiO_2 < 315 while on oxygen supplementation via standard nasal cannula or oxygen mask with reservoir bag"

2. Authors will use ROX index and lung ultrasound scores to predict the intolerance rate, this is the first time I have ever seen to use ROX index and lung ultrasound scores to predict the intolerance for HFNC or NIV, authors please explain the rationale.

This is our proposed hypothesis. If the ROX index or lung ultrasound scores are worse, we may be able to predict patients' intolerance as the worsening scores infer that the symptoms of heart failure have not alleviated and may have progressed. If we can predict such circumstances, the evidence can guide us to use these scores to better monitor patients with ACPE.

3. For NIPPV group, what oxygen device will be used in the break of NIPPV sessions? Will HFNC be allowed to use in-between NIPPV?

Due to resource constraints, only low-flow oxygen delivering device will be allowed during breaks of NIPPV or HFNC sessions if required. We have added to the intervention section the following statement; "Should the participants require breaks from either HFNC or NIPPV sessions, oxygen via standard nasal cannula or oxygen mask with reservoir bag will be delivered."

VERSION 2 – REVIEW

REVIEWER	Hugo de Carvalho Universite de Nantes - Faculte de Medicine, Emergency Medicine
REVIEW RETURNED	19-Feb-2022

GENERAL COMMENTS	Thank you for giving me the opportunity to review this revised version. The authors have made valuable changes to their manuscript, significantly improving the quality of the protocol. I wish them the best in conducting this study which might help us improve patients care. I recommend this manuscript to be accepted for publication.

REVIEWER	Jie Li Rush University, Cardiopulmonary Sciences, Division of Respiratory Care
REVIEW RETURNED	22-Jan-2022

GENERAL COMMENTS	I appreciate the authors took my suggestions. Most of my comments are addressed, but I still have two comments shown below: 1. For the exclusion of non-ACPE patients, even though the authors explained that the mITT analysis. However, I still have the concerns. If the patients need immediate respiratory support and the authors could not differentiate ACPE with other disease, such as airway disease, I think the authors should exclude those patients, otherwise it would affect study quality. 2. I appreciate the authors took my suggestions and modified the SF criteria. did the authors start recruiting patients? if so, I am concerned changing the inclusion criteria after recruiting patients would affect the study quality.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Dr. Jie Li, Rush University

Comments to the Author:

I appreciate the authors took my suggestions. Most of my comments are addressed, but I still have two comments shown below:

1. For the exclusion of non-ACPE patients, even though the authors explained that the mITT analysis. However, I still have the concerns. If the patients need immediate respiratory support and the authors could not differentiate ACPE with other disease, such as airway disease, I think the authors should exclude those patients, otherwise it would affect study quality.

We appreciate your concern regarding the matter. We do agree that having too many patients to be excluded later may hamper the interval validity of the study. Based on a previous randomized controlled trial conducted at our ED in the same patient population comparing HFNC with conventional oxygen therapy, we employed the same inclusion and exclusion criteria, and we found 4 out of 136 (2.9%) patients were excluded due to airway diseases (pneumonia) in the mITT analysis (http://dx.doi.org/10.1016/j.annemergmed.2017.03.028). We considered the proportion as acceptable especially when considering the true clinical implication of the study. In real clinical scenario, it may not be possible to rule out all other diseases at ED arrival. Applying such device to relieve dyspnea in patients with very high suspicion of ACPE thus should be appropriate. If other airway diseases are the primary provisional diagnosis, we shall exclude those patients. Consequently, we have added an exclusion criteria for “patients with other airway diseases as the primary provisional diagnosis”.

2. I appreciate the authors took my suggestions and modified the SF criteria. did the authors start recruiting patients? if so, I am concerned changing the inclusion criteria after recruiting patients would affect the study quality.

We appreciate your concern. The study just started recruiting its first patient on May, 5 2022. It has been delayed due to the COVID-19 pandemic. Therefore, we have made the correction for the previous revision before the first patient was recruited. Also due to an early phase of the study at the present time, adding an exclusion criteria based on your first query will not affect the study as there has not been one patient whose primary diagnosis is not ACPE included.

Reviewer: 2

Dr. Hugo de Carvalho, Universite de Nantes - Faculte de Medicine

Comments to the Author:

Thank you for giving me the opportunity to review this revised version. The authors have made valuable changes to their manuscript, significantly improving the quality of the protocol.

I wish them the best in conducting this study which might help us improve patients care.

I recommend this manuscript to be accepted for publication.

We appreciate the time and effort you have provided in improving the quality of our protocol.