PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	High-flow nasal cannula oxygen therapy alone or with noninvasive ventilation during the weaning period after extubation in ICU: the prospective randomised controlled HIGH-WEAN protocol
AUTHORS	Muller, Grégoire; Gacouin, Arnaud; Coudroy, Rémi; Demoule, Alexandre; Sonneville, Romain; Beloncle, François; Girault, C; Dangers, Laurence; Lautrette, Alexandre; Cabasson, Séverin; Rouze, Anahita; Vivier, Emmanuel; Le Meur, Anthony; Ricard, jean-damien; Razazi, Keyvan; Barberet, Guillaume; Lebert, Christine; Ehrmann, Stephan; Picard, Walter; Bourenne, Jeremy; Pradel, Gael; Bailly, Pierre; Terzi, Nicolas; Buscot, Matthieu; Lacave, Guillaume; Danin, Pierre-Eric; Nanadoumgar, Hodanou; Gibelin, Aude; Zanre, Lassane; Deye, Nicolas; Ragot, Stéphanie; Frat, Jean-Pierre; Thille, Arnaud

VERSION 1 – REVIEW

REVIEWER	Nuttapol Rittayamai Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
REVIEW RETURNED	13-May-2018

GENERAL COMMENTS	This is very interesting study protocol to compare HFNC and NIV-HFNC in patients after extubation with high-risk for extubation failure (i.e. elderly, underlying cardiac or pulmonary disease). The subject will be randomized to receive HFNC alone or NIV plus HFNC between NIV sessions and the main outcome will be the rate of extubation failure within 7 days. I have some comments and suggestions to the investigators as follows; 1. As we know that different SBT technique may affect SBT and extubation outcomes then using same SBT technique for all centers (instead of allowing each center to use their own SBT technique) may help to avoid the confounding factor from the different SBt technique. 2. The duration of HFNC in the control group on page 8 should be 48 hours (not 24 hours). 3. How the temperature will be set during HFNC treatment? (one important mechanism of HFNC is the heated and humidified gas that may enhance the secretion clearance then this factor should be controlled) 4. Please correct the study timeline for including patients (2017-2018??) on page 11 (I'm not sure whether the study has already started to enroll patients or not). 5. Because HFNC may be a key factor for success in this study. Do the investigator plan to perform subgroup analysis regarding the duration of HFNC use in the NIV group?

REVIEWER	Rafael Fernandez Althaia Xarxa Assistencial Universitaria de Manresa. Spain
REVIEW RETURNED	16-May-2018

GENERAL COMMENTS	Thille et al. presented the protocol of multicenter randomized clinical trial. The objective is to test whether noninvasive ventilation (NIV) added to high flow nasal cannula (HFNC) may reduce reintubation compared with HFNC alone. The research question is of clear interest and most of the project is correct. My main suggestion for the authors is to better describe outcomes. Your criteria no. 2 for moderate respiratory failure is the same that for severe respiratory failure ((2) Clinical signs suggesting respiratory distress with increase in the work of breathing and/or respiratory fatigue including activation of accessory respiratory muscles). Whereas for “moderate” at least 2 criteria are needed, for “severe” only one is enough and leading to reintubation. What will be the real decision for such a patient? Moreover, a PaO2/FiO2 <100 criteria to decide reintubation is probably too exaggerated compared with the “standard of care”, reducing the external validation of the study. It is not clear the reason for including a composite secondary outcome (moderate or severe acute respiratory failure) if all “severe” are already included in “reintubation”. Is this a “patient-oriented” outcome? Additional comments: - Please add your point-by-point CONSORT checklist. - Figure 1 and 3 should be melted in a single one, as a CONSORT flowchart. - Introduction and Table may be clearer and up-to-date if referenced to the meta-analysis of Bajaj et al. (Efficacy of noninvasive ventilation after planned extubation: A systematic review and meta-analysis of randomized controlled trials. Heart Lung. 2015 Mar-Apr;44(2):150-7) with more studies and summary of effects. - Page 12. Line 26. I suspect that your sentence: “The final model will include variables significantly associated with mortality” should be “with reintubation”.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Nuttapol Rittayamai
Institution and Country: Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below
This is very interesting study protocol to compare HFNC and NIV-HFNC in patients after extubation with high-risk for extubation failure (i.e. elderly, underlying cardiac or pulmonary disease). The subject will be randomized to receive HFNC alone or NIV plus HFNC between NIV sessions and the main outcome will be the rate of extubation failure within 7 days.
I have some comments and suggestions to the investigators as follows;

1. As we know that different SBT technique may affect SBT and extubation outcomes then using same SBT technique for all centers (instead of allowing each center to use their own SBT technique) may help to avoid the confounding factor from the different SBT technique.
Response: We fully agree that SBT technique may affect extubation outcome. However, although the work of breathing is significantly different between a spontaneous breathing trial performed with T-tube or pressure-support [1], no study demonstrated a difference in terms of outcome and especially reintubation rates [2]. Moreover, the type of weaning trial is often different form a center to another and thus to facilitate inclusions and adherence to protocol we decided to keep the usual weaning trial in each center. However, the type of weaning trial is obviously collected and we planned to adjust our results on this variable as indicated in the statistical methods: We will also perform a subgroup analysis according to the existence of any underlying cardiac or lung disease, age, severity scores, type of spontaneous breathing trial, clinical parameters at the end of the spontaneous breathing trial, cough assessment, amount of secretions, use of steroids, and weaning difficulty (simple, difficult or prolonged).

2. The duration of HFNC in the control group on page 8 should be 48 hours (not 24 hours).
Response: You are right. Thank you very much for detecting this mistake. We corrected.

3. How the temperature will be set during HFNC treatment? (One important mechanism of HFNC is the heated and humidified gas that may enhance the secretion clearance then this factor should be controlled)
Response: It is a very important concern and we added in the methods: To provide sufficient humidification the temperature of the heated humidifier will be set as during invasive mechanical ventilation, i.e. at 37°C.

4. Please correct the study timeline for including patients (2017-2018??) on page 11 (I'm not sure whether the study has already started to enroll patients or not).
Response: Inclusions started in 2017. We corrected as following: 2017: inclusion of patients;

5. Because HFNC may be a key factor for success in this study. Does the investigator plan to perform subgroup analysis regarding the duration of HFNC use in the NIV group?
Response: You are right. As patients in the HFNC/NIV group will receive NIV or HFNC, prolonged duration of HFNC means short periods of NIV. One of the main criticisms in our previous study on HFNC is the relative short durations of NIV [3]. During the weaning period, several studies reported durations of NIV of around 16-18h overt the first 24 hours [4 5]. Therefore, we decided to promote long periods of NIV with an objective of at least 12h/day during the first 48 hours. We agree with you and we added that we will a subgroup analysis among the assess the impact of NIV on reintubation in patients who will actually receive at least 12 hours of NIV during the first 24hours. We added in the statistical methods: As the duration of NIV may have an impact on outcome we will also perform a subgroup analysis among patients having actually received at least 12 hours of NIV during the first 24 hours (dose recommended by the study protocol).

Reviewer: 2
Reviewer Name: Rafael Fernandez
Institution and Country: Althaia Xarxa Assistencial Universitaria de Manresa, Spain
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thille et al. presented the protocol of multicenter randomized clinical trial. The objective is to test whether noninvasive ventilation (NIV) added to high flow nasal cannula (HFNC) may reduce

reintubation compared with HFNC alone. The research question is of clear interest and most of the project is correct.

My main suggestion for the authors is to better describe outcomes. Your criteria no. 2 for moderate respiratory failure is the same that for severe respiratory failure ((2) Clinical signs suggesting respiratory distress with increase in the work of breathing and/or respiratory fatigue including activation of accessory respiratory muscles). Whereas for “moderate” at least 2 criteria are needed, for “severe” only one is enough and leading to reintubation. What will be the real decision for such a patient?
Response: As indicated in the text severe ARF needs also 2 criteria: Severe acute respiratory failure defined by the presence of at least 2 criteria for severe respiratory failure among the following: (1) Respiratory rate > 35/min, (2) Clinical signs suggesting respiratory distress with increase in the work of breathing and/or respiratory fatigue including activation of accessory respiratory muscles, (3) Respiratory acidosis defined as pH < 7.25 units and $PaCO_2$ > 45 mm Hg, (4) Hypoxemia defined as a need for $FiO_2 \geq 80\%$ to maintain $SpO_2 \geq 92\%$ or $PaO_2/FiO_2 \leq 100$ mm Hg.
Moderate and severe include clinical signs of respiratory distress but all others criteria are different (RR 25 vs. 35 breaths/min; pH 7.35 vs. 7.35, and PF < 150 vs. PF < 100).

Moreover, a PaO_2/FiO_2 <100 criteria to decide reintubation is probably too exaggerated compared with the “standard of care”, reducing the external validation of the study.
Response: I am very sorry but I don’t agree. We chose this criterion according the literature. In the largest studies performed on the weaning by Esteban and colleagues, the criterion for hypoxemia was defined as a PaO_2/FiO_2 <120 [2 6], i.e. very close to ours. In your recent studies on high-flow during the post-extubation period the criteria for intubation indicated in the supplement was SpO_2 < 85% with a FiO_2 > 50% [7 8]. As SpO_2 85% corresponds to a PaO_2 value around 50-55 mm Hg, you therefore used a threshold value of PaO_2/FiO_2 < 100 in your own studies.
As patients treated with NIV may have a PF ratio higher than those treated with HFNC alone, we decided to use hard criteria for hypoxemia, and between 100 or 120 we chose 100.

It is not clear the reason for including a composite secondary outcome (moderate or severe acute respiratory failure) if all “severe”are already included in “reintubation”. Is this a “patient-oriented” outcome?
Response: We probably were not clear enough. We did not include a composite secondary outcome. Our secondary outcomes include the proportion of patients who will develop moderate acute respiratory failure and the proportion of patients who will develop severe acute respiratory failure. You are right that patients who will develop severe ARF should be intubated but that might not be the case (use of NIV as rescue therapy for example).
We clarified:
Secondary outcome variables include the following:
1. Reintubation at 48h, 72h and up until ICU discharge
2. An episode of moderate acute respiratory failure within the 7 days following extubation
3. An episode of severe acute respiratory failure within the 7 days following extubation

Additional comments:
- Please add your point-by-point CONSORT checklist.
Response: As required by the editor, we now provide the SPIRIT checklist.

- Figure 1 and 3 should be melted in a single one, as a CONSORT flowchart.
Response: Thank you very much for this comment. We changed the figure as suggested.

- Introduction and Table may be clearer and up-to-date if referenced to the meta-analysis of Bajaj et al. (Efficacy of noninvasive ventilation after planned extubation: A systematic review and meta-analysis of randomized controlled trials. Heart Lung. 2015 Mar-Apr;44(2):150-7) with more studies and summary of effects.
Response: All studies reported in the meta-analysis and indexed in PUBMED are included in our table. Our table aim to report the main randomized controlled trials but it is not a meta-analysis. Therefore, studies not indexed in PubMed or abstracts are not included in the table. We added the summary effects of the meta-analysis above-mentioned in the introduction: A meta-analysis of randomised controlled trials also suggests that prophylactic NIV may decrease reintubation rates in this population.[9]

- Page 12. Line 26. I suspect that your sentence: "The final model will include variables significantly associated with mortality" should be "with reintubation"
Response: You are right. Thank you very much for detecting this mistake.

References

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3. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185-96 doi: 10.1056/NEJMoa1503326[published Online First: Epub Date]|.
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5. Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. American journal of respiratory and critical care medicine 2006;173(2):164-70
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9. Bajaj A, Rathor P, Sehgal V, et al. Efficacy of noninvasive ventilation after planned extubation: A systematic review and meta-analysis of randomized controlled trials. Heart & lung : the journal of critical care 2015;44(2):150-7 doi: 10.1016/j.hrtlng.2014.12.002[published Online First: Epub Date]|.

VERSION 2 – REVIEW

REVIEWER	Dr. Nuttapol Rittayamai Division of Respiratory Diseases and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

REVIEW RETURNED	18-Jul-2018

GENERAL COMMENTS	The authors have already responded my comments/suggestions. I satisfied with the revised protocol and I have no further comment. Congratulatios!