Author’s response to reviews

Title: Can high-flow nasal cannula reduce the rate of reintubation in adult patients after extubation? A meta-analysis

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Author’s response to reviews:

Dear Editor,

Re: Manuscript ID PULM-D-17-00137R1

We would like to thank BMC PULM MED for giving us the opportunity to revise our manuscript.

We thank the reviewers for their careful read and thoughtful comments on previous draft.

We have carefully taken their comments into consideration in preparing our revision, which has resulted in a paper that is clearer, more compelling, and broader. The following summarizes how we responded to reviewer comments.

Below is our response to their comments.

Thanks for all help.

Best wishes,

Dr. Liang Zongan
Corresponding Author

Reviewer reports:

Masaji Nishimura (Reviewer 1): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

A meta-analysis of NIV use in selected subgroups of such patients suggests that judicious use of NIV may shorten ICU and hospital length of stay, reduce incidence of pneumonia, and improve hospital survival. As yet, for patients who undergoing major abdominal surgery, evidence is inadequate to confirm the benefit or harm of NIV during the postoperative period. HFNC has become more and more widely adopted for patients with different kinds of respiratory failure. While HFNC is better tolerated by patients, it was considered to be less effective than NIV via face mask. HFNC was considered superior to conventional oxygen therapy. Recently some clinical trials of HFNC for postextubation respiratory failure performed, although results were variable. Ni Y-N performed meta-analysis and evaluated if HFNC reduced the rate of reintubation in adults after extubation. Methodology was fine. Six RCTs were selected and meta-analysis was performed. The authors concluded HFNC reduced rate of reintubation compared with conventional oxygen therapy.

Basic profiles of patients in 6 RCTs varied. Corley included patients with BMI >30 and MV duration < 36 hours. Maggiore compared venturi mask and HFNC in patients of MV > 24 hours. Parke recruited patients after elective cardiac surgery who were extubated before 10:00 am next day. Conventional oxygen therapies also varied among the studies.

Meta-analysis is a strong strategy. However, same to NIPPV, HFNC does not necessarily work for all kinds of respiratory failure. Hernandez separately reported effect of HFNC between low and high-risk of reintubation, and the results were different. Kang reported HFNC unnecessarily prolonged worsened outcomes. It is more important to know kind of respiratory failure HFNC reduces mortality.

Answer:

Thank you for your advice. However, the studies included in our study enrolled patients with different underlying diseases and we could not do subgroup analysis because the limited number of studies for each categories, we could not suggest which kind of patients would routinely benefit from HFNC. We have mentioned it in the limitations of our manuscript.
Gonzalo Hernandez (Reviewer 2): First meta-analysis on this topic with positive results supporting the role of high-flow oxygen therapy for preventing reintubation.

Well performed and written paper. I have some major concerns:

- I know authors included papers published in the timeframe ranging from 1946 to July 2016, but in my opinion, some important papers have been published shortly after this range: Eg. OPERA trial (Oct/2016); Fernandez R, Ann Intensive Care 2017. I understand authors, but submission has been delayed 1 year and the risk of missing some important papers is relevant.

Answer:

Thank you for your advice, we have re-searched for the electronic database. And we have included the two papers in our study. All the figures and tables have been revised accordingly.

- ABSTRACT: results and conclusions is confusing: Eg. ... Compared with COT, HFNC was associated with lower rate of intubation, and the same result was found in the comparison between NIPPV. Eg. Conclusion: HFNC is a reliable alternative of NIPPV to reduce rate of reintubation compared with COT.

Answer:

Thank you for your careful reading and meaningful suggestion. We have revised our manuscript to make it clearer.

- BACKGROUND: ... NIPPV may prevent post-extubation respiratory failure and avoid reintubation [8-12]: in my opinion, the new guidelines should be cited, as report a strong recommendation for preventive NIPPV after extubation in high-risk patients.

Answer:

Thank you for your advice, we have added the new guidelines in our manuscript.

- RESULTS: Heterogeneity: ... No statistical heterogeneity was found... In my opinion, statistical heterogeneity can be safely excluded but a comment on clinical heterogeneity should be added: Eg. the analysis regarding reintubation rate compared to COT includes two trials on general critical care population and two centered on patients after cardiac surgery, with clearly different results. And the same for the OPERA trial, with negative results in patients after abdominal surgical intervention. HFNV seems to work differently after surgical patients at low risk for failure.

Answer:

Thank you for your advice. We have revised our manuscript and added the explanation about the heterogeneity in the Discussion part.
CONCLUSIONS: ... Compared to COT, HFNC could reduce... I consider that a meta-analysis like this one with positive results should not conclude with "could", but a stronger word.

Answer:

Just as the reviewers mentioned, statistic heterogeneity was found in our study. In addition, the study enrolled in our analysis involved in patients with different underlying diseases, and different reasons for respiratory failure. It is not very clear about the accurate target patients of HFNC. Thus, the “could” may be more appropriate in our study.

MINOR COMMENTS: refs 9 and 10 have some spelling errors (Ferrer M instead of FeORer M).

Answer:

Sorry our carelessness, we have revised our manuscript accordingly.

Teresa Renda, MD, PhD (Reviewer 3):

COMMENTS TO THE AUTHORS

This metha-analysis addresses a challenging clinical topic which appears to be somewhat conflicting in the literature.

Major comments

Please verify the results reported in the abstract and in the results, there are some discrepancies.

Answer:

Sorry for our carelessness, we have revised our manuscript accordingly.

Page 3 (PDF version), markers 25-29. "Compared with COT, HFNC was associated with lower rate of reintubation (Z=3.57, P=0.0004), the same result was found in the comparison between NIPPV (Z=0.87, P=0.38)"

Answer:

Sorry for our poor English, we have revised our manuscript and made it clearer.

Subjects considered in the selected studies for this metha-analysis had not well-balanced characteristics (heterogeneity of causes of ARF, selected adults with acute hypoxemic respiratory failure with different risk of reintubation, different primary outcome of studies). In light of above considerations, please clarify the following sentences:
Corley and his colleagues conducted a randomized controlled trial in 155 patients after cardiac surgery, and they found that HFNC could not decrease rate of treatment failure compared with conventional oxygen therapy (COT) (Odds ratio [OR] 0.53, 95% confidence interval [CI] 0.11-2.24, P=0.40). [15] On the contrary, a recent randomized trial by Hernández demonstrated that, compared with COT, HFNC could reduce the risk of reintubation among extubated patients (4.9% vs. 12.2%, P=0.004). These two mentioned studies (Corley A. Intensive Care Med 2015;41(5):887-94; Hernandez G. JAMA 2016; 315(13): 1354-61) are not comparable for both the design and the characteristics of subjects included in the studies.

Answer:

Thank you for your meaningful advice. We have read the enrolled studies again and selected the studies with similar design and characteristics of subjects (Fernandez 2017 and Hernández 2016). In addition, the relevant content has been modified in Background part.

Please specify the other potential risk of bias and the limitations of the studies taken into consideration. Some limitations are represented by measurements used for oxygenation assessment and oxygen therapy interface, inclusion of patients with non-hypercapnic hypoxemic ARF and from various aetiologies with different risk of reintubation and post-extubation ARF. All these limitations should explain the different results of the RTCs and the results reported by different meta-analysis (Maitra S et al. Journal of Critical Care 2016; 38: 138-144; Nedel WL et al. Resp Care 2016; 62 (1): 123-132; Corley A et al. 2017; DOI: 10.1002/14651858.CD010172.pub2).

Answer:

Thank you for your meaningful suggestion. We have added all these limitations into our manuscript.

In my opinion is mandatory to analyze all the studies with a similar primary endpoint such as post-extubation failure (reintubation). Some studies included in the meta-analysis have different primary endpoints (Corley et al. ICM 2015; Parke R et al. BJA 2013). Furthermore, in the study of Maggiore et al. ( AJRCCM 2014)

reintubation is a secondary endpoint.

Answer:

Thank you for your advices. We found in our analysis, reintubation was the primary endpoint in 3 studies(Herdanze 2016, Corley 2015, Parke 2013 ), and was secondary endpoint in 3 studies(Futier 2016, Ferdanze 2017, Maggiore 2014) when compared HFNC and COT. Thus, the number of study was not enough for us to do a subgroup analysis. We have added this point in the limitations of our manuscript.
To give more strength to your study you should highlight the difference of your data with those of the recently published meta-analysis.

Answer:
Thank you for your advice. We have added the comparison between our studies and others.

Discussion/Conclusion: The authors may suggest which kind of patients should routinely benefit from HFNC after extubation and the need to further investigate on the timing of HFNC (some studies limited HFNC to 24 hours post-extubation) and on the setting of flow parameters.

Answer:
Thank you for your advice. Based on the fact that the studies included in our study enrolled patients with different underlying diseases and set different flow of HFNC, and we could not do subgroup analysis because the limited number of studies for each categories, we could not suggest which kind of patients would routinely benefit from HFNC and the optimal flow.

Minor comments
Please check editing

Page 3 (PDF Version), marker 37: please replace reinubation with reintubation.

Page 4 (PDF Version), marker 13-15, markers 27-29: please verify the sentences ".......and barotrauma. And the hospital mortality of invasive mechanical ventilation remains as high as 30.7%. "; " ...... similar to those in mechanical ventilation, numerous potential hazards such as skin damage, eye irritation, interface intolerance, and diet and expectoration interruption ...."

Page 9-10 (PDF Version), marker 11-13: please report the reference related to the sentence "Hence larger end expiratory lung volume was observed in patients with HFNC than COT.".

Page 10 (PDF Version), marker 60-1: please verify the reference related to the sentence "Thereby HFNC can decrease respiratory rate and work of breathing [32. Tobin MJ et al. J Appl Physiol ]".

Page 10 (PDF Version), marker 25-27: Please revise this sentence: "Thus, the risk of the flow cannot satisfy the requirement of patients, which is common in COT, can be decrease".

Page 11 (PDF Version), marker 45: please replace retubation with reintubation.

Answer:
Sorry for our carelessness, we have revised item by item.