Author’s response to reviews

Title: The Effect of Sedation and/or Analgesia as Rescue Treatment during Noninvasive Positive Pressure Ventilation in the Patients with Interface Intolerance after Extubation

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Author’s response to reviews:

Dear Editor,

Re: Manuscript ID

We would like to thank BMC Pulmonary Medicine for giving us the opportunity to revise our manuscript.

We thank the reviewers for their careful reading 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.

Thanks for all help.

Best wishes,

Dr. Liang Zongan

Corresponding Author
Reviewer reports:

Franco Laghi (Reviewer 1):

In this retrospective investigation, Yue-Nan Ni et al studied 80 patients who had received noninvasive positive pressure ventilation (NIPPV) after extubation and who had experienced interface intolerance. Specifically the investigators assessed whether sedation and/or analgesia could reduce the rate of NIPPV failure (i.e., reintubation and reinstitution of mechanical ventilation) among those 41 out of 80 patients with interface intolerance who received sedation and/or analgesia. Secondary outcomes included in-hospital mortality and length of ICU stay after extubation.

Sedation and/or analgesia protected patients from NIPPV failure and death and reduced length of ICU stay after extubation. Accordingly, Yue-Nan Ni et al conclude that "using sedation and/or analgesia in patients with interface intolerance after extubation during NIPPV may offer advantages including in decrease of both the rate of NIPPV failure, hospital mortality and ICU LOS for these patients."

Major comments

The investigators state that "all adult patients received NIPPV after extubation were screened". It would be very informative if the investigators could let their readers know what are the usual criteria to start NIPPV in their ICUs.

Answer:

Thank you for your suggestion. In our study, all the patients used NIPPV directly after extubation. We have added the details about it in our paper.

Patients were eligible if "they were recorded as interface intolerance in the case history and/or nursing records and received more than 2h of NIPPV after extubation." The problem with this study, as with any retrospective study, is that we cannot know how good the documentation of health-care professionals was. We do not know how many more patients were not tolerant to the interface. We do not know what intolerance meant from one health-care professional to the next. These points need to be discussed in the manuscript.
Answer:

All the ‘interface intolerance’ were complained by patients themselves. In our ICUs, the RTs and clinicians would ask the patients whether he or she could tolerate the interface routinely when started the NIPPV and then record the results. What makes us regret is that we could not ensure all the patients with interface intolerance were recorded due to the data were retrospective collected. Thus, we have revised the Discussion part and discussed this point.

The most fundamental question I had after reading this paper is why some intensivists would chose to start sedation and/or analgesia and why others would not. Is this a matter of preference by a group of doctors? Is this something that has to do with patients’ characteristics not picked up by the phenotype characterization provided by the investigations? Please explain... Can you find out if sedation-analgesia occurred more often in a certain institution or with a certain group of intensivists rather than another one?

Answer:

Thank you for your question. There is little evidence about whether sedation and/or analgesia could benefit patients with interface intolerance or not, and in view of the current research status, the present study was conducted to address this question. In order to avoid the selective bias as far as possible, we have searched the medical records from all the ICUs with different medical teams in our hospital. Although we have collected all the data of the patients recorded as “interface intolerance”, it is a pity that the reason for “someone used the sedoanalgesia while the others did not” was not recorded. As is shown in Table 1, there is no difference between the two groups. We have revised the discussion to remind this limitation. Further random control trial is warranted to reduce the selection bias.

The investigators report that "in the unadjusted analysis, sedation and/or analgesia was significant associated with failure of NIPPV (29% vs. 59%, p=0.015)". It is only after correcting for confounders that sedation and/or analgesia comes ahead. I am concerned about this result. The investigators must provide a very strong rationale on why they chose one confounder vs. another confounder. That a confounder was associated with a p<0.10 on univariate analysis is not a sufficient reason to generalize the results of this study to other ICUs.

Answer:

Thank you for your question. We referenced some similar papers such as Hernández 2016(JAMA), Esteban 2002(JAMA) to choose the statistical method. After filtering with a p<0.10 on univariate analysis, a confounder used at last was discussed in the research group whether it has clinical sense.


The use of the medical English can be improved

Answer:

Thank you very much for careful reading and meaningful advice. We have polished our manuscript according to your advice.

Specific comments

Abstract ("...whether sedation and/or analgesia can benefit the clinical outcome of the patients with interface intolerance is still unclear"): You must specify which interface you are referring to.

Introduction ("… Patients with short duration of NIPPV were excluded to guard against reverse causality these groups of patients were already discontinued from the NIPPV when sedation and/or analgesia play a role"): I do not understand what you mean. Please, rephrase.

Discussion ("…the rate of delirium can be lowered when using sedation and/or analgesia ..."): The rate of delirium can also be increased when using sedation and/or analgesia.

Answer:

Thank you for your careful reading, and we have revised our manuscript item by item.

1) We have clarified that all of the interface used in our study were total face mask.
2) Sorry for our poor description. We meant that using sedoanalgesia needs at least two hours to influence the result of NIPPV.[1] In other words, if patients discontinued from NIPPV within 2 hours, there were some other important factors, such as disease itself besides interface intolerance, which could contribute to the failure. Also, there were some other studies also held the same opinion with us. We have rewritten this sentence to be seen more clearly.

3) It is certainly that excessive sedoanalgesia (RASS<-3) would increase the rate of delirium.[2-3] However, in our study, all the RASS score in patients received sedoanalgesia was controlled in -2~2, which resulted in no excessive sedoanalgesia in our study.


Eusebi Chiner (Reviewer 2): PULM-D-16-00483. The Effect of Sedation and/or Analgesia as Rescue Treatment during Noninvasive Positive Pressure Ventilation in the Patients with Interface Intolerance after Extubation

The authors studied retrospectively patients with interface intolerance who received noninvasive positive pressure ventilation (NIPPV) after extubation with a primary outcome as rate of NIPPV failure (defined as need for reintubation and mechanical ventilation) and a second outcomes included in hospital mortality and length of ICU stay after extubation. The study conclude that using sedation and/or analgesia in patients with interface intolerance after extubation during NIPPV may offer advantages including in decrease of both the rate of NIPPV failure, hospital mortality and ICU LOS for these patients.
A 2-year period in 7 hospitals in China with the inclusion of 80 patients and 41 finally analysed and compared seems a very poor number of patients to study and to draw conclusions.

Answer:

I think there is some mistake. The study was done in 7 ICU wards in West China Hospital rather than 7 hospitals in China. Although we tried our best to screen all the medical records within the two years, only 80 patients met the inclusion criteria in our study. We would like to conduct a random control trial in future with larger sample size.

SD not included in some outcomes such as age or hospital stay

Answer:

Thank you for your advice, and we have revised our manuscript accordingly.

We do not know if to compare groups, the patients were matched by age, BMI, gender, etc. This would have been more correct.

Answer:

Thank you for your question. Because it was retrospective study, we could not match the patients according the basic characteristics. But as is shown in Table 1, the characteristics, such as the age, gender, etc., did not differ between groups.

The protocol for administration of analgesia or sedation is not shown.

Answer:

We are really sorry for this. Because this study was a retrospective study, we could not make a protocol for administration of sedoanalgesia before the study. Please see responses to comments from reviewer 1 for details. We have discussed this point in the limitations.

The authors affirmed that in the unadjusted analysis, sedation and / or analgesia was significant associated with failure of NIPPV but after adjusting for sex that sedation and / or analgesia reduced the rate of NIPPV failure. I do not understand how or why this adjustment was made. The OR from the comparisons are insignificant from my point of view.

Answer:
As mentioned in the answer to Reviewer 1, the method of univariate analysis in our study was the same with Hernández 2016 (JAMA), Esteban 2002 (JAMA). And we did the adjustment in order to avoid the influence of confounding factors and increase the application of our conclusions.

There are quite number of grammatical errors in the manuscript.

Answer:

Sorry for it, we have polished our manuscript with Dongtao Lin’s (College of Foreign Languages and cultures, Sichuan University) help.

The discussion is long, speculative and difficult to read. The authors speculate about patient-ventilator asynchrony but do not show any monitoring data in this sense.

Answer:

Thank you for your meaningful advice, and we also think the information about patient-ventilator asynchrony could better reflex the advantages of sedoanalgesia on patients with interface intolerance. Unfortunately, the monitoring data such as Vt, RR was not specific to reflex the patient-ventilator asynchrony. Based on the related research (Ramirez 2017), the patient-ventilator asynchrony could be judged by observing the flow wave timely, but it is very hard for clinicians recording. And because it was a retrospective study, we had no chance to collect information about patient-ventilator asynchrony.


Jacek Nasiłowski, MD, PhD (Reviewer 3): The study "The Effect of Sedation and/or Analgesia as Rescue Treatment during Noninvasive Positive Pressure Ventilation in the Patients with Interface Intolerance after Extubation" touches on an interesting topic about the role of sedation in the treatment with non-invasive ventilation. The major finding of the study of Yue-Nan Ni et al. is that sedation and/or analgesia should be used in patients who require NIPPV after extubation and do not tolerate the interface, because it reduces the risk of re-intubation and death, and shortens the stay in ICU.
However, the retrospective, observational methodology of the research limits the strength of the results and the conclusions must be withdrawn with caution. The important methodological drawbacks have to be fixed before potential publication. More details concerning methods of treatment of the cohort are needed to improve the drawing of conclusions.

The points of criticism are as follows:

1. In Abstract:
   a. the most important results (mortality, need for intubation) should be incorporated into the text, giving only an adjusted odd ratio is not enough.
   b. Statement "some time during NIPPV" must be defined and added to results

   Answer:
   a. Thank you for your meaningful advice, and we have revised the Abstract accordingly.
   b. We have defined the “some time” in the Method part. And the start and lasting time of sedoanalgesia varies from patient to patient because this was a retrospective study, we have discussed it in the limitations.

2. In Methods:
   a. The study design was retrospective, so authors could not say the study was conducted from December 2014 to August 2016, as patients hospitalized between December 2014 to August 2016 were included
   b. If I understand correctly: the authors were searching in medical records of the eligible subject. It must be clearly stated.
   c. The indications to start NIPPV after extubation that were followed must be given. Authors mention that ABG prior to NIPPV was performed but there is no such data in the results section.
   d. Interface intolerance is a very broad spectrum of problems: claustrophobia, inability to match an interface, high leakage, etc. Sometimes inefficacy of NIV itself may be addressed as mask intolerance. The authors should define what medical staff understood by the statement in the records: "interface intolerance".
e. The statement that ABG was recorded at the start and after 4 h of NIPPV suggests that there was a common protocol of treatment in all ICUs taking part in the study. Could they give more details about this protocol?

f. The criteria of failure of NIPPV and the need for intubation should be detailed.

g. What were the rules of administration of sedoanalgesia? Was it only in the discretion of the physician?

h. The kind of used interfaces must be detailed. Facial mask - does it mean an interface covering mouth, nose and eyes, e.g. Performax or total face mask?

Answer:

a. Thank you for careful reading, and we have revised it accordingly.

b. Thank you for the suggestion, and we have revised it.

c. In the study, we collected all the patients used NIPPV directly after extubation. We have added the indication details in our paper. And the ABG before NIPPV was just the one before extubation, which has been shown in the Table 1.

d. As mentioned above, the clinicians would ask for the feeling of patients during NIPPV, and the “interface intolerance” was complained by the patients themselves.

e. In our hospital, we have set up a standard operating procedure to manage the patients who were extubated which including to do a ABG 0.5h and 4h after NIPPV, and all the clinicians and RTs were trained to follow the protocol.[1] And if the respiratory status of patients was unstable, we would do extra ABG accordingly. The ABG 0.5h after NIPPV had been recorded in every patient’s document, but the 4h ABG would not be recorded if no parameter was abnormal. So, not every 4h ABG for patients was collected by us.


f. It has been added in the Method part.
g. Sorry for this. Because this is no consensus about the benefits of using sedoanalgesia in patients with interface intolerance after extubation during NIPPV, we could not know the whether it is suitable to give sedoanalgesia in such patients. Thus, we carried out this retrospective study to add some evidence about this question. Also, we have revised the limitations.

h. We have detailed it in the methods.

3. In the results section:
   a. 309 patients required NIPPV after extubation and only 80 were recorded as not tolerated an interface. Half of them had sedoalangesia. But sedation is not only indicated in the mask intolerance, but also in asynchrony and agitation caused by other issues than an interface. It would be useful if the authors gave information about administration of sedoanalgesia in the group not recorded as mask intolerance.

   b. The dosage and duration of administration of the drugs must be incorporated in the text or a table.

   c. In our study, all of the patients used NIPPV directly after NIPPV. And we have detailed it in our paper.

   d. The length of treatment with NIPPV until intubation or recovery should be given.

   e. The results of ABG half an hour after initiation of NIPPV shows no acidosis nor relevant hypercapnia and put in doubt the further use of NIPPV. ABG results just before starting NIPPV must be given.

   f. Are the authors sure that NIPPV was efficient while the pressure support was quite low: 8-9 cmH2O? Maybe the failure of NIPPV was due to low pressures not the asynchrony and "mask intolerance" caused by a lack of sedation?

   g. Table 4 is quite striking. It shows that patients with pneumonia and hypoxaemic respiratory failure had a higher risk of NIPPV failure, than patients with COPD and hypercapnia. This finding is rather obvious. NIPPV is mainly dedicated to ventilatory respiratory failure, while hypoxemic respiratory failure should be treated with NIPPV with caution and intubation should be undertaken as soon as there is no sign of improvement. This topic and the results in Table 4 have to be discussed by the authors.
Answer:

a. Because the aim of our study was to study whether sedoanagesia could improve the prognosis of patients received NIPPV with interface intolerance, we did not focus on the issues of sedoanalgesia on patients without interface intolerance. We also agree it is interesting to compare the use of sedoanalgesia in patients with or without interface intolerance in future research.

b. Because it was a retrospective study and the dosage as well as lasting time was variable due to the clinical status changed momentarily, we are really sorry that we have no chance to collect the data. We has discussed this problem in the limitation.

c. We have added the details in our paper.

d. We have added it in the Result and discussed it.

e. The aim of NIPPV was providing respiratory support. Good ABG results means the parameter and support level is suitable and successful. On the contrary, if ABG shows acidosis or relevant hypercapnia during NIPPV, it indicates that the support level is not enough, or we can think the NIPPV is failing and we should increase the support level of NIPPV or prepare to intubation. Patients with good respiratory status when using NIPPV did not mean that they could maintain this status after weaning from the NIPPV. We adjusted the parameter of NIPPV after every ABG in order to decrease the support level of NIPPV and discontinue it as soon as possible follow the protocol (Please see the NIPPV protocol we added in the paper).

f. In our study, there is no difference on the mean pressure support levels between the two groups (sedoanalgesia and nonsedoanalgesia) (IPAP: p=0.639, EPAP: 0.599) and some other characteristics between the two groups did not differ. All of the patients received NIPPV after extubation when the initial disease result in respiratory failure had been resolved. In our study, NIPPV was applied to the patients not because of disease itself but because of low ability of airway protection and cough strength.[1] Moreover, some other studies also showed that the support level just as in our study was enough.[2]


g. Thank you for your careful reading, and the study also showed that NIPPV would be more effective in patients with COPD and hypercapnia. We have revised our manuscript and discussed it.