Author's response to reviews

Title: Role of sedation for agitated patients undergoing noninvasive ventilation in clinical practice in a single hospital

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Dr. Antonio Esquinas
Associate Editor
BMC pulmonary medicine

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Title: Role of sedation for agitated patients undergoing noninvasive ventilation in clinical practice

Dear Dr. Antonio Esquinas

We wish to thank you for your email of March 31, 2015, regarding our manuscript, "Role of sedation for agitated patients undergoing noninvasive ventilation in clinical practice" and for the careful reading of our manuscript and the very useful comments. We have revised the manuscript on the basis of your comments.

Sincerely yours,

Our responses to the reviewers’ comments as well as your comments are as follows.

Responses to the comments of the editor

Associate Editor:

This article is original and highlights information for making decisions in clinical practice. However, some major aspects need to reorganize to appropriate second evaluation.

1. Selection criteria: need present more clearly.
2. Statistical analysis: need present more clearly.
3. Conclusions: need to more precise

Thank you very much for your valuable comments.
According to the comments of the Section Editor and the Reviewers, we revised our manuscript.
1. Selection criteria: To present the information more clearly, we revised the selection criteria as follows.

1) Patients (page 6, line 88-page 7, line 104)

“Our hospital is a 700-bed tertiary care center that plays a central role in treating emergency patients in the surrounding area. Among consecutive patients over 16 years old who underwent continued NIV due to acute respiratory failure from May 2007 to May 2012, we retrospectively evaluated patients who received sedatives for agitation during NIV.

We assigned patients to 3 groups; one group received sedatives only intermittently (intermittent only), a second group was switched to continuous sedation after intermittent sedation (switched to continuous) and the third group was initially sedated continuously (initially continuous). According to code status, we also classified patients into non-DNI and DNI groups. Patients in the non-DNI group were intubated and mechanically ventilated if control was not achieved by NIV, while patients in DNI group were continuously controlled by NIV and were not intubated even if consciousness deteriorated following sedation or their conditions became critical. Code status of neurologically incompetent patients was determined by discussion with relatives. When patients or their families did not want to be ventilated (including NIV) or their baseline status was difficult to maintain with NIV, we suggested that they not be ventilated from the viewpoint of ethics.”

2) Noninvasive ventilation (page 7, line 110-page 8, line 127)

“NIV was started when 1) SpO$_2$ was $<90\%$ despite inhalation of oxygen $>10$ l/min via reservoir mask; 2) PaCO$_2$ levels were $>45$ mmHg with acute respiratory acidosis; or 3) patients had signs of respiratory distress, including a respiratory rate $>24$ and increased accessory respiratory muscle use. Patients were managed with NIV in the ICU, emergency ward, or general ward by expert respiratory staff. NIV was performed with a Drager ventilator (Carina; Drager, Lübeck, Germany) or Philips ventilator (Respironics V60 or Respironics BiPAP Vision; Philips, Andover, MA, USA) with the pressure support ventilation (PSV) mode or continuous positive airway pressure (CPAP) mode via a full face mask. The ventilator setting and selection of either the CPAP or PSV mode were generally determined based on the criteria for initiation of NIV described above. The PSV was selected if a patient met criterion 2) and/or 3), but if a patient had only hypoxemia and met criterion 1), we selected the CPAP mode. For the PSV mode, the initial setting was a respiratory rate of 12 breaths/min, inspiratory
positive airway pressure of 10 cm H\textsubscript{2}O, and expiratory positive airway pressure of 4 cm H\textsubscript{2}O. For the CPAP mode, the first setting was a positive end expiratory pressure of 8 cm H\textsubscript{2}O. The FiO\textsubscript{2} was adjusted to keep the SpO\textsubscript{2} >90%. After the start of NIV treatment, NIV settings were modified by physicians proficient in NIV treatment according to each patient’s condition.

3) Sedatives (page 8, line 130-page 9, line 135)

“For intermittent use, risperidone or haloperidol was usually administered every 30-60 min by either a single dose or double dose (Table 1). For continuous use, either dexmedetomidine, midazolam, or propofol was the initial choice. Physicians in this hospital preferred to use a short-acting drug or a drug with a minimal respiratory depressant effect. When despite sedation dyspnea could not be controlled, we used morphine or fentanyl to alleviate the dyspnea.”

4) Criteria for the beginning of sedation and administration of sedatives (page 9, lines 138-149)

“When NIV was started according to the criteria described above, we used the Richmond Agitation Sedation Scale (RASS) [13] as an index of sedation for controlling agitation. Sedatives were administered when patients could not continue NIV due to agitation, and generally, +1 or more on the RASS was defined as an indication to administer sedation. Patients were most often managed between -2 and 0 on the RASS during sedation. Usually, sedation was initiated intermittently and if the target sedation level was not achieved, we began continuous administration. However, continuous sedation was introduced initially when physicians judged that intermittent sedation would not be sufficient to control agitation. At that time the attending physicians set the target range for the RASS, which was most often measured by medical staff. When the RASS deviated from the established range, the infusion rate was adjusted as shown in Table 1. When good control was not achieved with the first sedative, another was added.”

2. According to the suggestion of Reviewer 1, we used the Mann-Whitney test for the analyses of continuous variables. We changed Table 4 and the Methods section as follows (page 11, lines 168-169).

“Continuous variables are expressed as mean ± standard deviation unless stated otherwise and were compared using the Mann-Whitney test.”
3. According to your comment and that of Reviewer 2, we revised the Conclusion section as follows.

In the Abstract (page 4, lines 51-54):
“According to RASS scores, sedation during NIV in proficient hospitals may be favorably used to potentially avoid NIV failure in agitated patients, even in those having diseases with poor evidence of the usefulness of NIV. However, we were unable to demonstrate the safety of sedation in agitated patients undergoing NIV.”

In the text (page 19, lines 313-321):
“Our results suggest that sedation during NIV can be used to enable continuation of NIV in agitated patients with either a DNI or non-DNI status with management according to RASS, even in patients with diseases for which there is little evidence of the usefulness of NIV. However, conclusion could not be made regarding the safe use of sedatives with NIV for agitated patients because of the low number of patients within the subgroups studied, the large number of drugs used, and the heterogeneity of the drugs in term of pharmacokinetics and pharmacodynamics. It should be taken into consideration about the indication for sedation in each patient and the setting in which it is provided (general wards or ICU) because it depends on the proficiency or system of each institution.”

Section Editor:
in the response mail I would stress the fact that the paper has important drawbacks so that a very large revision is needed before considering it for publication:
1) As underlined by reviewer 2 the choice of the drug and its regimen (intermittent or continuous) is not clear and this is a really crucial point

Thank you very much for your review and valuable comments. We appreciate your opinion.
We apologize for the insufficient explanation regarding the choice of drug and regimens for their use in the previous version.
We changed the Methods section as follows (page 8, line 129-page 9, line 149).

“Sedatives
For intermittent use, risperidone or haloperidol was usually administered every 30-60 min by either a single dose or double dose (Table 1). For continuous use, either dexmedetomidine, midazolam, or propofol was the initial choice. Physicians in this hospital preferred to use a short-acting drug or a drug with a minimal respiratory depressant effect. When despite sedation dyspnea could not be controlled, we used morphine or fentanyl to alleviate the dyspnea.

Criteria for the beginning of sedation and administration of sedatives

When NIV was started according to the criteria described above, we used the Richmond Agitation Sedation Scale (RASS) [13] as an index of sedation for controlling agitation. Sedatives were administered when patients could not continue NIV due to agitation, and generally, +1 or more on the RASS was defined as an indication to administer sedation. Patients were most often managed between -2 and 0 on the RASS during sedation. Usually, sedation was initiated intermittently and if the target sedation level was not achieved, we began continuous administration. However, continuous sedation was introduced initially when physicians judged that intermittent sedation would not be sufficient to control agitation. At that time the attending physicians set the target range for the RASS, which was most often measured by medical staff. When the RASS deviated from the established range, the infusion rate was adjusted as shown in Table 1. When good control was not achieved with the first sedative, another was added.”

2) other methodologic aspects are really poorly cared -i.e. criteria for starting sedation: (according to Richmond scale??), physiologic data concerning the starting of NIV are confused (ph?? paO2/fiO2 ratio??); setting of the ventilator and choice of CPAP or NIV is not reported;

We appreciate your suggestions and apologize for the deficiencies in the explanation of the methodologic aspects in the previous version. According to your suggestion, we revised the explanation of the criteria for initiating NIV, ventilator settings, and selection of CPAP or PSV (page 7, line 109-page 8, line 127). Our response regarding the criteria for starting sedation is given in comment 1).

“Noninvasive ventilation

NIV was started when 1) SpO2 was <90% despite inhalation of oxygen >10 l/min via reservoir mask; 2) PaCO2 levels were >45 mmHg with acute respiratory acidosis; or 3) patients had signs of respiratory distress, including a respiratory rate >24 and
increased accessory respiratory muscle use. Patients were managed with NIV in the ICU, emergency ward, or general ward by expert respiratory staff. NIV was performed with a Drager ventilator (Carina; Drager, Lübeck, Germany) or Philips ventilator (Respironics V60 or Respironics BiPAP Vision; Philips, Andover, MA, USA) with the pressure support ventilation (PSV) mode or continuous positive airway pressure (CPAP) mode via a full face mask. The ventilator setting and selection of either the CPAP or PSV mode were generally determined based on the criteria for initiation of NIV described above. The PSV was selected if a patient met criterion 2) and/or 3), but if a patient had only hypoxemia and met criterion 1), we selected the CPAP mode. For the PSV mode, the initial setting was a respiratory rate of 12 breaths/min, inspiratory positive airway pressure of 10 cm H$_2$O, and expiratory positive airway pressure of 4 cm H$_2$O. For the CPAP mode, the first setting was a positive end expiratory pressure of 8 cm H$_2$O. The $\text{FiO}_2$ was adjusted to keep the $\text{SpO}_2 > 90\%$. After the start of NIV treatment, NIV settings were modified by physicians proficient in NIV treatment according to each patient’s condition.”

3) as suggested by reviewer1 the setting of the ward is inappropriate and unsafe to treat with NIV under sedation pts with diseases showing low chances of success (i.e. hypoxemia de novo);

We appreciate your opinion and that of Reviewer 1. In the revised text as shown below, we have clarified this situation with regard to our institution. As we mentioned, the medical staff at our institution is highly experienced in NIV treatment. This personnel is able to intubate promptly and apply mechanical ventilation in respiratory wards, if needed, during NIV treatment. But we did not have data on a sufficient number of patients to make a definitive conclusion on the safety of NIV treatment with sedatives; therefore, as you and Reviewer 1 pointed out, we apologize for the possibility that readers might be misled. We have addressed these concerns through the following revision (page 17, lines 283-289).

“In this study, sedation during NIV treatment was introduced to 31% of the study patients in the general wards, and in most of these patients treatment could be continued in the general wards. Many members of the medical staff of our hospital are highly experienced in NIV treatment so that NIV with sedatives could be controlled in general wards. However, as we did not have data on a sufficient number of patients to make a definitive conclusion on the safety of NIV treatment with sedatives, NIV
treatment with sedatives should be applied cautiously and at present should be performed in an ICU.”

4) It’s not clear how DNI status has been defined in neurologically incompetent pts (choice by the authors? shared with relatives?); in DNI-pts did the author explore the possibility of do-not-ventilate (including NIV) according to ethical point of view?

Thank you for calling this point to our attention. We revised the Methods section as follows (page 7, lines 100-104).

“Code status of neurologically incompetent patients was determined by discussion with relatives. When patients or their families did not want to be ventilated (including NIV) or their baseline status was difficult to maintain with NIV, we suggested that they not be ventilated from the viewpoint of ethics.”

5) The largest published paper dealing with use of sedation under NIV is not reported (Rocco et al Intensive Care Med 2010)

Thank you for providing this information.
We added the new reference (Rocco M et al. Intensive Care Med 2010,36:2060-2065) , which suggested that a remifentanil-based sedation protocol can decrease the rate of failure in patients with intolerance to NIV, in the Introduction section and Discussion section as follows (page 15, lines 250-252). We changed the number of the other references.

“Previous studies have addressed the efficacy of sedation during NIV using dexmedetomidine[6-8], midazolam[8], propofol[9], and remifentanil[10] in patients with several diseases in which there was a high-to-intermediate level of evidence for NIV use.”

5) English requires a large editing!

We revised the English extensively. Our revised manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by physicians whose native language is not English.
Responses to the comments of Referee 1

The present study deals with an interesting and important issue topic: the role of sedation in patients treated with noninvasive ventilation (NIV) for acute respiratory failure. Although confusion and agitation represent so far a relative contraindication for NIV if we consider guidelines, the authors have shown that sedation may contribute to NIV success especially in patients with a low literature evidence for NIV indication based on their underlying disease.

It is an original work and the findings are interesting but please find my comments below.

Major comments:

1. Why did you further classify your patients in DNI and non-DNI? It is unclear what value this classification adds to the paper in order to meet your primary aim; moreover it may reduce your sample size,

Thank you very much for your review and valuable comments. We appreciate your opinion.

As you pointed out, the further classification of study patients into DNI and non-DNI group reduced the sample size. However, we felt that this classification was needed because the implications for sedation are different in DNI and non-DNI groups. Physicians usually perform intubation with mechanical ventilation when the NIV treatment is not effective in non-DNI patients who are treated with NIV. For DNI patients, intubation with mechanical ventilation is not applied when the NIV treatment is ineffective. That is, in the light of respiratory management, failure to control agitation would become fatal, and continuing NIV treatment with sedation is critical in the DNI group. On the other hand, in the non-DNI group, when we cannot continue NIV, we can perform intubation and continue mechanical ventilation. So we do not necessarily persist in continuing NIV treatment, and sedation is optional. Therefore, we thought that the differences in the usage of sedatives between DNI and non-DNI patients might be informative to readers. We changed Discussion section as follows (page 16, lines 260-271).

“In this study, patients were divided into two groups; DNI and non-DNI groups. Although this resulted in a small sample size for analysis in some groups, we thought that differences in the usage of sedatives between DNI and non-DNI patients might be
informative to those managing NIV treatment with sedatives. When NIV treatment is not effective in non-DNI patients, physicians usually choose intubation with mechanical ventilation. However, in DNI patients, intubation with mechanical ventilation is not performed when NIV treatment is not effective. That is, in the light of respiratory management, failure to control agitation would become fatal, and continuing NIV treatment with sedation is critical in the DNI group. On the other hand, in the non-DNI group, when we cannot continue NIV, we can perform intubation and continue mechanical ventilation. So we do not necessarily persist in continuing NIV treatment, and sedation is optional."

2. I would reconsider the message that sedated patients on NIV for acute respiratory failure (who may required intubation at their worsening) can be safely managed in a respiratory ward as stated by the authors (Page 14, Line 9), please consider to better explain this concept in order to avoid misleading message to the readers.

We appreciate your opinion and that of the Section Editor. In the revised text as shown below, we have clarified this situation with regard to our institution. As we mentioned, the medical staff at our institution is highly experienced in NIV treatment. This personnel is able to intubate promptly and apply mechanical ventilation in respiratory wards, if needed, during NIV treatment. But we did not have data on a sufficient number of patients to make a definitive conclusion on the safety of NIV treatment with sedatives, and as you and the Section Editor pointed out, the previous version might be considered inappropriate. We apologize for the possibility that readers might be misled. Therefore, we revised Discussion section as follows (page 17, lines 283-289).

"In this study, sedation during NIV treatment was introduced to 31% of the study patients in the general wards, and in most of these patients treatment could be continued in the general wards. Many members of the medical staff of our hospital are highly experienced in NIV treatment so that NIV with sedatives could be controlled in general wards. However, as we did not have data on a sufficient number of patients to make a definitive conclusion on the safety of NIV treatment with sedatives, NIV treatment with sedatives should be applied cautiously and at present should be performed in an ICU."

2. Statistical analysis: I couldn't find in the statistical analysis the normal distribution check of t-test (ie. Shapiro-Wilks or Q-Q Plot). Moreover there is a difference in the
number of cases in the non-DNI group between intermittent and continuous sedation (28 vs. 11). I suggest you to use a more robust non-parametric test like Mann-Whitney.

Thank you for your comments.
We had checked the distribution of normality of each parameter by the Shapiro-Wilk test, and we used the t-test for the analysis of age in DNI group. As you suggested, we used the Mann-Whitney test for the analyses of continuous variables.
We changed Table 4 and the Methods section as follows (page 11, lines 168-169).

“Continuous variables are expressed as mean ± standard deviation unless stated otherwise and were compared using the Mann-Whitney test.”

Minor comments:
1. Page 5 Line 4, I suggest to use a present tense.
We changed the sentence to a present tense as follows (Page 5, lines 65-68).

“Although NIV usage is not strictly indicated for agitated or uncooperative patients[3, 4], a questionnaire to pulmonologists and intensivists showed that 85% of such patients had been sedated while under NIV, with 30% receiving continuous sedation, suggesting its usefulness in clinical practice[5].”

2. Page 10 Line 15, I suggest avoid letters to express numbers, in order to be consistent throughout the manuscript.
We changed the expression of the sentence you pointed out, and deleted the specific numbers as follows (Page 12, lines 190-193).

“Table 3 shows the prescribed sedatives. Twenty-four (50%) patients received a single drug and the remaining patients received more than one drug for continuous use. With the exception of risperidone or haloperidol, hydroxyzine, quetiapine, diazepam or perospirone was used intermittently.”

3. Table 1 label: change the semicolon with a full stop.
We changed the semicolon of the Table 1 label with a full stop.

Responses to the comments of Referee 2

The authors studied the "Role of sedation for agitated patients undergoing noninvasive ventilation in clinical practice" an important and well known issue.

Major Compulsory revisions:
The question posed by the authors is focused on the efficacy and safety of sedation for agitated patients undergoing NIV in clinical practice. They retrospectively reviewed sedated patients who received NIV due to acute respiratory failure from May 2007 to May 2012 choosing numerous different drugs used alone or with a second drug, intermittently or switched to continuous or in a continuous infusion from the beginning. The patients were also divided as DNI or non-DNI procedure. The analysis of these data are really difficult or impossible as the number of the patients in the subgroups are really low and heterogeneous for the large number of drugs used and their large heterogeneity in term of pharmacokinetics and pharmacodynamics. The take home message is too general: sedation during NIV could be feasible.

Thank you for your valuable comments. According to your informative suggestions, we revised the conclusion as follows.

In the Abstract (page 4, lines 51-54):
“According to RASS scores, sedation during NIV in proficient hospitals may be favorably used to potentially avoid NIV failure in agitated patients, even in those having diseases with poor evidence of the usefulness of NIV. However, we were unable to demonstrate the safety of sedation in agitated patients undergoing NIV.”

In the text (page 19, lines 313-321):
“Our results suggest that sedation during NIV can be used to enable continuation of NIV in agitated patients with either a DNI or non-DNI status with management according to RASS, even in patients with diseases for which there is little evidence of the usefulness of NIV. However, conclusion could not be made regarding the safe use of sedatives with NIV for agitated patients because of the low number of patients within the subgroups studied, the large number of drugs used, and the heterogeneity of the
drugs in term of pharmacokinetics and pharmacodynamics. It should be taken into consideration about the indication for sedation in each patient and the setting in which it is provided (general wards or ICU) because it depends on the proficiency or system of each institution.”

We also changed the Methods and Discussion sections extensively.

Additional Editorial Requests:
1. Name of Ethics Committee:

Please update your ethics statement to include the name of the ethics committee that approved your study.

We included the name of the ethics committee that approved this study (page 7, lines 105-107).

“This study was approved by our institutional review board (Institutional Review Board of Kobe City Medical Center General Hospital; 1304-1), and informed consent was waived.”

2. Copyedit:

We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

We revised the English extensively. Our revised manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing
papers written by physicians whose native language is not English.

3. Track Changes:

Please also highlight (with 'tracked changes'/coloured/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt final decision on your manuscript. We prefer if you can make text look like it was marked with a highlighter pen the modified part of the original manuscript.

We have highlighted all changes made when revising the manuscript.

Thank you again for your valuable comments on our paper. We trust that the revised manuscript is suitable for publication.

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