Author's response to reviews

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

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Dr. Antonio Esquinas  
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Title: Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital

Dear Ms Hazel Joyce Delos Santos and Dr. Antonio Esquinas

We wish to thank you for your email of May 14, 2015, regarding our manuscript, "Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital" and for the careful reading of our manuscript and the very useful comments. We have revised the manuscript on the basis of your comments.

The attached paper entitled “Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital” 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.

Sincerely yours,

Responses to the comments of the editor

Editor's Comments:

I appreciated a lot the efforts of the authors in sorting out all the pertinent concerns raised by the reviewers and by myself.

Unfortunately, aims and presentation of the results seem to be still confused. Specifically, there are some topical points that needs to be clarified by the authors:

1) the purpose of the study sounds to evaluate in the clinical practice of an expert center the "efficacy" and "safety" of sedation in an heterogeneous population with ARF. a-Does efficacy of sedation means only that the
patients could be exposed to NIV for a longer time as compared to non-sedated independently on the outcome (i.e. comfort, intubation, mortality, complications)? In other words, is prolong of NIV thanks to sedation always a favorable effect for the patient? Looking at the results of the study, despite only 4% of the population failed for persistent agitation, the rate of intubation (in non-DNI subgroup) and the mortality rate (in DNI subgroup) were really consistent, respectively about 30% and ranging from about 60 to 80%! Should the clinicians reach the target of "NIV at all costs" also in non-tolerant patients with demonstrated poor outcome with NIV (i.e. hypoxemic ARF, diffuse lung diseases etc.)

Thank you very much for your review and valuable comments. As you say, the purpose of this study was to evaluate the efficacy and safety of sedation during NIV in clinical practice. In this study, efficacy of sedation was considered to be defined by the avoidance of NIV failure. In the non-DNI group, failure of sedation was declared when a patient was intubated due to agitation in spite of sedation, and failure of sedation in the DNI group was declared when NIV treatment could not be continued due to agitation.

We added the following explanation in the Methods section (page 10, lines 161-165). “In this study, the avoidance of NIV failure was considered to indicate the efficacy of sedation. In the non-DNI group, failure of sedation was declared when a patient was intubated due to agitation in spite of sedation, and failure of sedation in the DNI group was declared when NIV treatment could not be continued due to agitation.”

In our study, sedation during NIV enabled 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. Therefore, we considered that sedation during NIV was effective. However, we do not think that continuing NIV was always a favorable decision, especially in the non-DNI group. In that group, when we could not continue NIV, we could intubate the patient and provide mechanical ventilation. For this reason, we do not necessarily persist in continuing NIV treatment in such patients, as explained on page 17, lines 281-284. On the other hand, in DNI patients, failure to control agitation would become fatal due to acute respiratory failure; therefore continuing NIV treatment with sedation is critical. Thus, sedation during NIV may help DNI patients, as explained on page 17, lines 278-281.
As you pointed out, the mortality rate in the DNI group was high. Unlike in Western countries, in Japan, most patients are divided according to NIV treatment or intubation with ventilation, although some remain without any ventilatory support as in other countries. Therefore, although there is the possibility that sedation itself increases mortality, in Japan, when a patient cannot make decisions we usually provide NIV to those with a DNI status according to the family’s will, even when the baseline status is too poor for rescue or there is little evidence of NIV’s usefulness for the background disease. Many patients in the DNI group were severely ill and tended to become agitated and need sedation. Therefore, we often had to continue NIV with sedation as palliative care, which might contribute to some degree to the high mortality rate.

We had removed this information in the first revised version, but have now added this information to the newly-revised version as shown below (page 17, line 295-page 18, line 302).

“In Japan when a patient cannot make decisions we usually provide NIV to those with a DNI status according to the family’s will, even when the baseline status is too poor for rescue or there is little evidence of NIV’s usefulness for the background disease. Many patients in the DNI group were severely ill and tended to become agitated and need sedation. Therefore, we often had to continue NIV with sedation as palliative care, which might contribute in some degree to the high mortality rate. However, we must consider the possibility that the continuous sedation itself increased the mortality rate.”

In the non-DNI group, the rate of intubation was about 30%. Although the rate of intubation differed according to the baseline diseases and their severities, the failure rate of sedation defined as the application of intubation in this study was little different from those in previous reports (Garpestad E et al. Chest 2007;132:711-720, Mas A et al. Int J Chron Obstruct Pulmon Dis 2014;11:837-852, AIYami MA et al. Ann Thorac Med 2015;10:16-24).

So, when taken together, our emphasized point about efficacy was that sedation during NIV could 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. In non-DNI patients, we should avoid delaying intubation due to persistence in administering sedatives during NIV, but in DNI patients, continuing NIV treatment in agitated patients would be important in terms of respiratory management and sedation might help in this effort to continue NIV treatment.
b-what does the authors intend for "safety" of sedation? if we consider that mortality rate is Greater in continuous vs intermittent sedation and a similar behavior was reported for PaCO2 levels in DNI-subgroup, the authors have to convince me that sedation is feasible to make patients to carry on with NIV even when NIV is likely to fail. Should we also consider ethical issues: could be the way to ?push NIV at all costs? in patients who refuse it a chance to prolong agony for several patients with DNI pts?

As mentioned in comment 1)a, in Japan, when a patient is not able to make decisions and the family has decided upon a DNI status, we usually provide NIV even when the baseline status is too poor for rescue or there is little evidence of NIV’s usefulness for the background disease. Many patients in the DNI group were severely ill and tended to become agitated and need sedation. Therefore, we often had to continue NIV with sedation as palliative care, which might have contributed to some degree to the high mortality rate in the continuous use group of DNI patients. The change in the PaCO2 level within 24 hours after the initiation of sedation was significantly greater in the continuous use group than in the intermittent use group, but this condition improved after increasing pressure support. Those that largely deviated from the target sedation levels were the patients with hypercapnia before sedation. On the other hand, 36 patients in the switched to continuous group could continue NIV treatment by continuous sedation (Figure 1 and Table 5). This is the merit of continuous sedation, especially in the DNI group whose respiratory treatment cannot proceed to mechanical ventilation with intubation.

However, although we could continue NIV treatment with the aid of continuous sedation, we have to pay attention to the hypercapnic state and the possibility of increased mortality in administering sedatives during NIV. Because there were no control patients, further study is needed to elucidate the merits and demerits of continuous sedation, especially with regard to mortality.

We changed the Conclusion section as follows (page 20, lines 334-341).

“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, we must be aware of the possibility of an increased hypercapnic state and high mortality rate associated with continuous sedation, which may be due to the sedation itself. In addition, 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 much depends on the proficiency or system in each institution.”

As to ethical issues, when patients or their families did not want ventilation to be provided (including NIV) or the patient’s baseline status was difficult to maintain with NIV, we suggested that ventilation not be provided from the viewpoint of ethics, as explained on page 7, lines 104-106. Although discontinuing NIV would be fatal, if after starting NIV the patient or family wanted to discontinue NIV treatment, we did so (As shown in Table 5, 3 patients discontinued NIV treatment).

2) Honestly, sedation in the ward without monitoring as message for the reader does not convince me again: how could clinicians detect risks of oversedation and side effects (i.e hypotension, delirium, worsening of blood gases) early enough to avoid serious risk for the patient in a un-monitorized area, especially for non-DNI cases?

As you say, sedation without monitoring is not safe. We did not mean to imply that monitoring was not necessary. In our hospital, we had large separate rooms for patients who needed intensive care in a general ward. When we performed NIV treatment in a general ward, we put the patient in such a room. We also monitored SpO₂ and heart rate of sedated patients around the clock as in an ICU. Medical staff frequently checked patients’ condition and general consciousness.

We changed the Methods section as follows (page 8, lines 116-117).
“Patients in a general ward were put in large separated rooms for intensive care and monitored 24 h per day.”

3) Schedule of NIV is not reported: I could just read in the Table 4 that NIV was delivered for about 4 to 10 days. But how many hours a day? According to which criteria?

We apologize for this insufficient explanation. Since NIV was performed in patients with acute respiratory failure, treatment was provided for 24 hours per day. When NIV treatment was not needed for 12 consecutive hours, NIV treatment was considered to be finished. We made the following change to the Methods section (page 8, lines 130-132).
“At first NIV treatment was performed all day, and when NIV treatment was not needed consecutively for 12 h, NIV treatment was considered to be finished.”
4) What are the reasons for poor tolerance before sedation: agitation, mask discomfort, decubitus? and when, immediate, after some hours or days of NIV?

The reasons for poor tolerance of NIV before sedation was almost always mask discomfort, pressure discomfort, or a combination of both. Most of these problems occurred immediately after the start of NIV treatment.

We changed the Results section as follows (page 12, lines 189-191).

“The reasons for poor tolerance of NIV were mostly mask discomfort, pressure discomfort, or the combination of the two. Most expressions of poor tolerance occurred immediately after the start of NIV treatment.”

5) When the authors preferred to use drugs with preeminent analgesic (i.e. opioids) properties respect to pure sedative (i.e. benzodiazepine or propofol) or anti-psycotic drugs (risperdone)?

We generally used risperidone or haloperidol for intermittent sedation, and dexmedetomidine, midazolam, or propofol for continuous sedation. However, when despite sedation dyspnea could not be controlled, we used an opioid to alleviate the dyspnea, as explained on page 9, lines 135-140.

5) I do not see data about changes of pH, PaO2/FiO2, PaCO2, Respir rate and haemodynamics and RASS over NIV time (i.e. 2 hours, 6 hours, 24 hours, subsequent days). Only changes of capnia over 24 hours are reported. It is a insufficient physiologic information to have an idea of the impact of sedation on NIV effectiveness. This is a crucial issue to evaluate again safety of sedation

Thank you for your instructive comment.

We reviewed the medical records again and added the physiologic information in the revised version. As to changes in the RASS score, respiratory rate, heart rate, and systolic blood pressure, there were no significant changes between the intermittent and continuous use groups, nor were there acute changes during the 24 hours (Additional file 1).

As to changes in pH and the PaO2/FiO2 ratio during 24 hours following the initiation of sedation, there were no significant differences in changes between the intermittent and
continuous use groups (Additional file 2).
Adverse effects during the entire period of sedation are shown in Table 6. Although data on arterial blood gas were insufficient due to the fact that this is a retrospective study, changes after sedation were similar between the intermittent and continuous use groups in terms of physiologic data.

We changed the Methods section as follows (page 10, lines 166-169).
“Physiologic values were monitored and the RASS score, respiratory rate, heart rate, and blood pressure were checked before sedation and as closely as possible to 2 h, 6 h, and 24 h after the start of sedation. Arterial blood gas changes during 24 h following the initiation of sedation were also checked.”

We also changed the Results section as follows (page 14, line 240-page 15, line 248).
“Before and after the start of sedation, the RASS score, respiratory rate, heart rate, and systolic blood pressure did not differ significantly between intermittent and continuous use groups, nor did acute changes occur during the 24 h from the start of sedation (Additional file 1).
The values of arterial blood gas were rechecked within 24 h from the start of sedation in 18 patients in the intermittent use group and 18 in the continuous use group. Changes in PaCO$_2$ levels were significantly greater in the continuous use group than in the intermittent use group (Figure 2). There were no significant differences in changes in pH and P/F ratio between groups (Additional file 2).”

6) As a matter of a fact the conclusions of the authors should be carefully calibrated on the aims of the study, considering that there is not a controlled arm: how could have been the outcomes if these patients (especially DNI subgroup with hypoxemia) would have been managed without NIV, e.g. with High Flow O2 therapy? I suggest to compare these data with an hystorical group of similar patients before the practice of sedation was implemented in the center for NIV.

In a previous report, the outcomes of DNI patients with hypoxemia were varied. In a previous study of DNI patients, the mortality rate was 37.5% in COPD patients, while in patients with hypoxemic respiratory failure the mortality rate was as high as 86% (Schettino G et al. Crit Care Med 2005;33:1976-1982; newly added as reference 18). Regarding DNI patients with hypoxemia treated with high flow therapy, the mortality rate was reported to be 60% (Peters SG et al. Respir Care 2013;58:597-600).
In previous reports of patients with acute exacerbation of interstitial pneumonia from 2004 to 2006, the mortality rate for NIV-treated patients in our hospital was reported to be 56% (Tomii K, et al. Intern Med 2010; 49: 1341-1347; reference 11), but the number of study patients was low. As we could not directly compare mortality with control patients, we must consider the possibility that the continuous sedation itself increased the mortality rate.

We changed the Conclusion section as follows (page 20, lines 334-341).

“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, we must be aware of the possibility of an increased hypercapnic state and high mortality rate associated with continuous sedation, which may be due to the sedation itself. In addition, 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 much depends on the proficiency or system in each institution.”

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

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