Peer review file

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Reviewer A

Comment 1: As authors outline in their introduction, remifentanil is an opioid with metabolism that is independent of renal and hepatic function. It is therefore a useful agent to treat pain in the ICU setting. However, the study design and proposition do not reflect the fact that remifentanil is not a sedative. It is commonly used as an adjunct to midazolam and propofol in sedation protocol. Therefore, the comparison of these two drugs should focus for cardiac surgery patients with moderate to severe noninvasive ventilation intolerance. The authors should expand their discussion section to explain that success with REM arm most likely rests in successful analgesia in patients who may have developed delirium in the setting of poorly controlled pain.

Reply 1: Thank you very much for the suggestions. Although there were articles describing remifentanil as sedative or analgosedative [1-5], "treatment" might be more suitable than "sedation" in this situation. We have made revisions as suggested. Also, we have expanded our discussion section as suggested.

Changes in the text: We replace "sedation" with "treatment" throughout the manuscript. Discussion section, paragraph 2: Also, preliminary studies have shown that REM and DEX were both effective for treatment of NIV-intolerance. On the one hand dexmedetomidine was able to treat delirium and guarantee comfort during NIV support, remifentanil on the other hand was able to control pain and reduce respiratory drive during NIV and allow the patient to cope with the ventilator.

Comment 2: The authors would benefit from grammar and stylistic review to address the writing overall. For example, "sedation regime" should be changed to "sedation regimen" throughout the article.

Reply 2: Thanks for your suggestion. We have polished our article by a native speaker.

Changes in the text: "Sedation regime" was changed to "treatment regimen", "is" was

changed to “was”, and other grammar mistakes were revised, as appropriate.

Reviewer B

Comment 1: NIV support is usually triggered by a thorough assessment, hopefully following recent ATS guidelines (2017) https://erj.ersjournals.com/content/50/2/1602426. Did the authors follow such recommendations? How did they assess the need for NIV rather than CPAP or reintubation?

Reply 1: Thank you for reminding this. In this study, NIV support was triggered by a thorough assessment, following ATS guideline (2017). And the criteria for NIV support in our center were as follows: (1) hypoxemia with a partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio of < 150 mmHg; (2) tachypnea with a respiratory rate (RR) of > 25 breaths/min for at least 2 h; (3) signs of increased work of breathing, use of accessory respiratory muscles, and/or paradoxical abdominal movement; and (4) sequential NIV after extubation for high-risk patients. For patients with cardiogenic pulmonary edema, NIV or CPAP were both recommended by the ATS guideline (2017). In this study, more than 90% of the patients were cardiogenic, and we adopted NIV for all patients to make sure the uniformity of enrolled patients.

In our center, NIV would be applied to the patients before resorting to reintubation, which was in consistent with the ATS guideline (2017). It was recommended by the ATS guideline (2017) that a trial of bilevel NIV could be considered before endotracheal intubation and mechanical ventilation, unless the patient is immediately deteriorating. The criteria for reintubation in this study were: (1) patient’s refusal to continue NIV due to persistent intolerance; (2) clinical signs of respiratory failure despite maximum NIV support; (3) the development of conditions requiring airway protection, such as coma, seizure, and copious tracheal secretions, etc.; (4) severe hemodynamic instability; and (5) life-threatening arrhythmia.

Changes in the text: In this study, NIV support was triggered by a comprehensive assessment, following American Thoracic Society guideline (2017). And the criteria for NIV support in our center were as follows: (1) hypoxemia with a partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio of < 150 mmHg; (2) tachypnea with a respiratory rate (RR) of > 25 breaths/min for at least 2 h; (3) signs of increased

work of breathing, use of accessory respiratory muscles, and/or paradoxical abdominal movement; and (4) sequential NIV after extubation for high-risk patients.

Comment 2: 100% FiO2 with either invasive or non-invasive support might lead to hyperoxia and further derangement. An explanation is needed.

Reply 2: Thanks again for mentioning this. Indeed, 100% FiO2 might lead to hyperoxia and further derangement. However, in this study, before initiation of NIV support, most of the status of patients were serious and immediate restoration was needed. As a result, we initiated the FiO2 to be 100%, and the ventilator settings, including FiO2, would then be titrated according to the patient's vital signs, tolerance, and/or arterial blood gas analysis.

Changes in the text: NIV was started with fractional inspired oxygen concentration of 100%, level of pressure support of 12 cm H2O and positive end expiratory pressure of 5 cm H2O. The ventilator settings were then titrated according to the patient's vital signs, tolerance, and/or arterial blood gas analysis.

Comment 3: Dexmedetomidine and remifentanil are completely different drugs: the first is an alpha 2 adrenergic receptor agonist that is similar to clonidine with enhanced properties regarding sedation; the latter instead is a powerful short acting opioid that might be applied to treat postoperative pain.
If on the one hand dexmedetomidine is able to treat delirium and guarantee comfort during NIV support, remifentanil on the other hand is able to reduce respiratory drive during NIV and allow the patient to cope with the ventilator.
The authors should provide detailed analysis regarding advantages and drawbacks following the administration of both drugs and the rationale for either use.

Reply 3: Thank you very much and this question is very important. The advantages and drawbacks of both drugs were shown in the table below[6]. In our center, both drugs were used for the sedation of cardiac surgical patients, and the drug of choice for treatment of NIV intolerance was decided by the bedside physicians, according to the patient's clinical status. For example, for patients with bradycardia or hemodynamic

instability, dexmedetomidine might not be chosen, and for patients with a full stomach, remifentanil might not be chosen. After administration of both drugs, NIV failure was avoided in about 80% of patients (REM: 81.8% and DEX: 79.9%). No patient was deeply sedated (RASS score ≤ 4) in this study. Chest wall rigidity was observed in one patient in the REM group, although spontaneous breathing resumed before SpO2 began to decrease. Vomiting was observed in one patient in the REM group, which was alleviated soon after intramuscular injection of 10 mg of metoclopramide. One patient in the DEX group required reintubation due to severe hemodynamic instability, which was eventually corrected at about 2 h after discontinuation of DEX.

Drug
Advantages
Drawbacks
Remifentanil
Ultra-short-acting opioids; quick onset and offset of effects;
Chest wall rigidity; vomit
Dexmedetomidine
α2-receptor agonist, anxiolytic, sedative, and analgesic effects
Profound bradycardia; severe hemodynamic instability

Changes in the text: Material and method section, paragraph 4: In this study, treatment for NIV intolerance was initiated when a NIS of 3 or 4 was recorded. The drug of choice was decided by the bedside intensivist, according to the patient's clinical status. Discussion section, paragraph 2: On the one hand dexmedetomidine was able to treat delirium and guarantee comfort during NIV support, remifentanil on the other hand was able to control pain and reduce respiratory drive during NIV and allow the patient to cope with the ventilator.

Comment 4: The authors correctly put in relationship efforts to breathe with cardiac dysfunction but this section in the discussion paragraph should be expanded.

Reply 4: We have expanded this section in the discussion paragraph as suggested.
Changes in the text: The major reason for NIV in this study was cardiac dysfunction,

which was characterized by increased work of breathing, manifesting as tachypnea with a high respiratory drive. According to the American Thoracic Society guideline (2017), NIV might be used as a ventilatory support for these patients.

Comment 5: Population section is repeated. I suggest the authors to merge both under material and method section.

Reply 5: This is a very good suggestion and we have made revisions accordingly.

Changes in the text: Result section, we merged population, perioperative characteristics and characteristics prior to treatment as characteristics for the enrolled patients.

Comment 6: Results are spread across multiple paragraphs I suggest the authors to revise the main text structure.

Reply 6: Thank you very much for the suggestion. And we have revised the main text structure as suggested.

Changes in the text: Result section, we merged population, perioperative characteristics and characteristics prior to treatment as "characteristics for the enrolled patients". Besides, we added difference of NIV failure in the "The time-dependent therapeutic effects of two treatments" paragraph.

Comment 7: English language should be revised by a native speaker.

Reply 7: We were very sorry for the poor language and have polished our manuscript by a native speaker. Many thanks for the suggestion.

Changes in the text: "regime" was changed to "regimen", "is" was changed to "was", and other grammar mistakes were revised, as appropriate.