Dexmedetomidine Versus Midazolam for the Sedation of Patients with Non-invasive Ventilation Failure

Zhao Huang, Yu-sheng Chen, Zi-li Yang and Ji-yun Liu

Abstract

Objective To compare the efficacy and safety of sedation with dexmedetomidine vs. midazolam for patients with acute cardiogenic pulmonary edema and hypoxemia during the treatment of non-invasive ventilation (NIV).

Methods The intensive care unit (ICU) patients treated in our hospital between March 2008 and August 2011 who had acute pulmonary edema and hyoxemia in NIV failure due to patient refusal to continue the NIV sessions (due to discomfort) were enrolled in this study. The patients were divided into two groups by the random numerical table method. They were treated with either midazolam (29 cases) or dexmedetomidine (33 cases). The patients were sedated (Ramsay scale 2-3) by a continuous perfusion of midazolam or dexmedetomidine during the NIV session. Cardiorespiratory and ventilatory parameters, the results of the blood gas analysis, and adverse events were prospectively recorded. The main outcome measure was the percentage of endotracheal intubation during NIV. Secondary endpoints included the duration of non-invasive mechanical ventilation, length of ICU stay, and adverse events.

Results In both groups of patients, the expected sedative scores were obtained. The cardiorespiratory symptoms and signs (oxygenation index, pH value, and respiratory rate) were significantly improved in both groups. In the dexmedetomidine-treated group, the patients had a further decreased percentage of failure of NIV requiring endotracheal intubation (ETI) and a more prolonged mean time to ETI (p=0.042, p=0.024). Furthermore, when compared with the group treated with midazolam, the overall duration of mechanical ventilation and the duration of ICU hospitalization in the group treated with dexmedetomidine were markedly decreased, and weaning from mechanical ventilation was easier (p=0.010, p=0.042). Despite the fact that more dexmedetomidine-treated patients developed bradycardia (18.2% vs. 0, p=0.016), no patients required an intervention or interruption of study drug infusion. Conversely, the incidence of respiratory infections and vomiting was lower in the dexmedetomidine-treated patients (p=0.026, p=0.010).

Conclusion Dexmedetomidine led to a more desired level of awakening sedation, shortened the duration of mechanical ventilation and the length of the ICU stay, and further reduced the prevalence of nosocomial infection for NIV sedation in patients with acute cardiogenic pulmonary edema. It appears to provide several advantages and safe control compared with the γ-amino butyric acid (GABA) agonist midazolam.

Key words: dexmedetomidine, midazolam, non-invasive ventilation, sedation, acute cardiogenic pulmonary edema

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Introduction

Recently, non-invasive mechanical ventilation (NIV) has been increasingly used to manage hypoxemic acute cardio-

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refusal to continue the often uncomfortable sessions. Although a lot of attention has been dedicated to the development of new interfaces with increased tolerance, mask intolerance and discomfort still represent a major cause for NIV failure (4). Antonelli et al. (5) showed that mask intolerance or inadequate patient cooperation led to intubation in 9% of patients with Acute Renal Failure (ARF). Carlucci and co-workers reported that when NIV was discontinued early (i.e. while the physician wished to continue it) the reason for discontinuation was the patients’ refusal to continue in 22% of cases (6). In this situation, the traditional option is to stop NIV and intubate the patients.

Some authors have reported the use of sedative agents to achieve adequate compliance with NIV. Providing sedation to improve the patients’ comfort is an integral component of bedside care for nearly every patient in the intensive care unit (ICU) (7, 8). In a preliminary study (9), Constantin et al. showed that remifentanil-based sedation during NIV is effective and safe in selected patients with NIV failure. For decades, β-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the most commonly administered sedative drugs for ICU patients worldwide (10, 11). Despite the well-known hazards associated with prolonged use of GABA agonists, few investigations of ICU sedation have compared these agents to other drug classes.

Dexmedetomidine is an α2 adrenoreceptor agonist with a unique mechanism of action, providing sedation and analgesia via receptors within the locus ceruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression (12, 13). Dexmedetomidine sedation was recently been proposed to manage NIV failure in acute respiratory failure patients in a preliminary study (14). We hypothesized that a sedation strategy using dexmedetomidine would result in improved outcomes in non-invasive mechanically ventilated, hypoxemic acute cardiogenic pulmonary edema ICU patients compared with the standard GABA agonist midazolam. To test this hypothesis, we observed 62 patients in our hospital ICU who received dexmedetomidine or standard sedation using midazolam infusions.

**Materials and Methods**

The experimental protocol was approved by our institutional review board for human subjects. Written informed consent was obtained from each study participant or their next of kin.

**Patient selection**

The study cohort consisted of 62 adult patients with acute cardiogenic respiratory failure under NIV. The inclusion criteria included: patients older than 18 years of age; signs and symptoms consistent with acute cardiogenic pulmonary edema; NIV failure due to patient refusal to continue NIV because of discomfort, claustrophobia or marked agitation. The exclusion criteria were: a poor respiratory state requiring immediate intubation; a clear alternative primary diagnosis such as pneumonia; severely altered consciousness; any patient requiring an immediate lifesaving intervention such as cardiopulmonary resuscitation, airway control, cardioversion or inotropic support; any patient requiring thrombolysis or percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. The flow of patient enrollment, randomization, and treatment is shown as Fig. 1. All the enrolled patients completed the study. Table 1 describes the patients’ characteristics and the baseline physiological data, including their cardiac and pulmonary condition. The left ventricular ejection fraction (LVEF) was calculated by echocardiography with Doppler ultrasound.
Non-invasive ventilation

All patients were noninvasively ventilated with a latex-free helmet (CaStar, Starmed, Mirandola, Italy) or a total face mask (Respironics, Monroeville, PA, USA) connected to Drager ventilator (Drager, Lubeck, Germany) in pressure support mode (PSV) with the noninvasive positive pressure ventilation (NPPV) software program. Pressure support ventilation was increased in increments of 2-3 cm H2O at 2- to 3-minute intervals over the first 10-15 minutes according to the clinical response and tolerance of the patient to obtain an exhaled tidal volume of 6-8 mL/kg and a respiratory rate (RR) lower than 35 breaths min⁻¹. The positive end-expiratory pressure (PEEP) was repeatedly increased by 2 cm H2O to a maximum of 10 cm H2O until the FiO₂ requirement was 65% or less to maintain the oxygen saturation above 92%. The ventilator settings were then adjusted on the basis of pulse oximetry and serial measurements of arterial blood gases. After this period and once the PEEP requirements decreased to 5 cm H₂O, each patient was evaluated daily while breathing supplemental oxygen without ventilatory support for 15 minutes. NPPV and drug sedation were reduced progressively in accordance with the degree of clinical improvement and were discontinued if the patient stably maintained a RR <25 breaths min⁻¹ and a PaO₂/FiO₂ >200.

Criteria for endotracheal intubation

The predetermined criteria for endotracheal intubation (ETI) were as follows: failure to maintain a PaO₂/FiO₂ ratio greater than 150, development of conditions requiring ETI to protect the airways (e.g., seizure disorder or vomiting); development of copious tracheal secretions; an increase in the partial pressure of arterial carbon dioxide accompanied by a pH of 7.20 or less; severe hemodynamic instability, defined as a systolic blood pressure of less than 70 mmHg; or evidence on electrocardiography of ischemia or clinically significant ventricular arrhythmias; patient refusal owing to persistent interface intolerance. The all-cause ETI was assessed and recorded after the administration of sedation from ICU admission.

Study drug administration

Eligible patients were randomized to receive dexmedetomidine or midazolam by the random numerical table method to obtain more comprehensive safety data. Midazolam was selected as the comparator medication because it is the only benzodiazepine approved for continuous infusion and is commonly used for long-term sedation in many countries, including the United States. Optional loading doses (up to 1 μg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator’s discretion. The starting maintenance infusion dose was 0.2-0.7 μg/kg per hour for dexmedetomidine and 0.05-0.1 mg/kg per hour for midazolam. The infusion rate was adjusted to maintain a target sedation level of a Ramsay score of 2-3. Sedation was stopped when the mechanical ventilation was discontinued.

Outcome measures and adverse events

The primary outcome variable was the need for ETI and mechanical ventilation at any time during the study. Secondary outcome variables included the length of stay and mortality in the ICU, the development of complications, and the duration of non-invasive mechanical ventilation in the patients who never required ETI.

Adverse events were assessed and monitored by the principal investigator and were recorded from the first dose of study drug until 48 hours after study drug discontinuation. The protocol pre-specified that bradycardia and hypotension were considered adverse events if the systolic blood pressure was less than 80 and diastolic blood pressure was less than 50, or the heart rate was less than 40/min. A greater than 30% change from the baseline heart rate or blood pressure was also considered an adverse event. Other adverse events included nausea, vomiting, aspiration and delirium.

Statistical analysis

All data are expressed as the medians ± SD. The mean difference between the dexmedetomidine and midazolam treatment groups were calculated and compared with the Mann-Whitney U test, while comparisons for the incidence of ETI and adverse events, and the mortality rate between the two groups was evaluated with a nonparametric two-tailed chi-squared test or Fisher’s exact tests when appropriate. The mean time to intubation in the patients who required ETI during the study and the length of non-invasive mechanical ventilation in the patients who never required ETI was calculated using a Kaplan-Meier survival analysis, with differences between treatment groups assessed by the log-rank test. Statistical tests were 2-sided, and p<0.05 was
Table 2. Primary and Secondary End Points in Patients Treated with Dexmedetomidine VS. Midazolam

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midazolam</th>
<th>Dexmedetomidine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of endotracheal intubations/total (%)</td>
<td>13/29(44.8)</td>
<td>7/33(21.2)</td>
<td>0.043</td>
</tr>
<tr>
<td>Mean time to ETI (h)</td>
<td>17.8±1.9</td>
<td>27.6±4.7</td>
<td>0.024a</td>
</tr>
<tr>
<td>Cause of ETI</td>
<td></td>
<td></td>
<td>0.565</td>
</tr>
<tr>
<td>Severe hypoxemia No.(%)</td>
<td>4/13(30.8)</td>
<td>2/7(28.6)</td>
<td></td>
</tr>
<tr>
<td>Copious tracheal secretions No.(%)</td>
<td>5/13(38.5)</td>
<td>1/7(14.3)</td>
<td></td>
</tr>
<tr>
<td>Severe hemodynamic instability No.(%)</td>
<td>1/13(7.7)</td>
<td>2/7(28.6)</td>
<td></td>
</tr>
<tr>
<td>Vomiting No.(%)</td>
<td>3/7(23.1)</td>
<td>2/7(28.6)</td>
<td></td>
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<tr>
<td>Secondary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>8.5±4.6</td>
<td>4.9±4.3</td>
<td>0.042</td>
</tr>
<tr>
<td>ICU Mortality(%)</td>
<td>3/29(10.3)</td>
<td>2/33(6.1)</td>
<td>0.658</td>
</tr>
<tr>
<td>Length of NIV in patients who never required ETI(h)</td>
<td>(n=16)</td>
<td>(n=26)</td>
<td></td>
</tr>
<tr>
<td>Physiology at 24h after sedation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>96.6±4.6</td>
<td>97.5±3.7</td>
<td>0.476</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.4±0.05</td>
<td>7.5±0.19</td>
<td>0.781</td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>271.4±36.0</td>
<td>289.9±25.2</td>
<td>0.397</td>
</tr>
<tr>
<td>Average dosage of sedative (mg.kg-1)</td>
<td>0.07±0.004</td>
<td>0.10±0.03</td>
<td></td>
</tr>
</tbody>
</table>

* Calculated using Kaplan-Meier survival analysis, with differences between treatment groups assessed by the logrank test.

Results

A total of 62 eligible patients were randomized and received the study drug. These comprised the primary analysis study population (33 patients received dexmedetomidine, 29 received midazolam). All the enrolled patients completed the study.

Description of patients and comparability between groups

The patients were elderly (mean age±SD: 61.5±7.3 vs. 67.4±8.2 years), predominantly female (59% vs. 57%) and unwell, with marked hypoxemia (PaO2/FiO2: 183.3±24.5 vs. 176.6±31.2), acidosis (PH: 7.22±0.2 vs. 7.23±0.1) and tachypnea (mean respiratory rate/min: 36±3 vs. 35±2). They had significant co-morbidities [ischemic heart disease (31% vs. 27.3), valvular heart disease (20.7% vs. 27.3%), chronic obstructive pulmonary disease (10.4% vs. 9.1%) and hypertension (27.6% vs. 27.3)]; the baseline characteristics were similar between treatment groups (Table 1).

Study drug administration and efficacy of sedation

The expected sedation scores (Ramsay score 2-3) were achieved in all of the patients taking dexmedetomidine or midazolam. The cardiorespiratory symptoms and signs (oxygenation index, respiratory rate and oxygen saturation) were significantly improved in all subjects in both groups. However, the patients who received dexmedetomidine were more easily aroused with adequate sedation.

Primary and secondary outcomes

Twenty out of 62 patients (midazolam vs. dexmedetomidine: 44.8%:21.2%, p=0.043 ) failed to continue the non-invasive treatment, requiring ETI after the administration of the drug. The median time to intubation was 27.6±4.7 h for dexmedetomidine vs. 17.8±1.9 h for midazolam (p=0.024), as shown by the Kaplan-Meier curve (Table 2, Fig. 2).

After analyzing the cause, it was determined that 6 out of the 20 failures in both groups were caused by the persistence of hypoxemia despite sedative infusion, which probably worsened, at least in part, by the concomitant persistence of an inability to increase the PaO2/FiO2 ratio above 180 mmHg. Conversely, 3 failures were owing to hemodynamic intolerance, and 6 failures to copious tracheal secretions. There were no significant differences in the cause of endotracheal intubation between the midazolam and dexmedetomidine groups (p=0.056).

All patients without ETI were weaned from NIV successfully in both groups. The duration of study drug treatment was shorter in the dexmedetomidine group because the dexmedetomidine-treated patients were weaned from NIV more rapidly (57.5±7.9 h vs. 93.4±12.4 h, p=0.01 by logrank) as estimated by the Kaplan-Meier method (Table 2, Fig. 3). The dexmedetomidine-treated patients also showed a shorter ICU stay (4.9±4.3 h vs. 8.5±4.6 h, p=0.042), but the ICU mortality was similar between the groups (10.3% for midazolam and 6.1% for dexmedetomidine; p=0.066).
which could be directly attributable to the ability to inde-
period were lower in the dexmedetomidine-treated patients,
patients with bradycardia required an intervention or interrup-
However, none of these dexmedetomidine-treated pa-
stopped study drug infusions because of adverse events.
recorded serious adverse events, and none of the patients
considered to be related to the study drug. There were no
The rates of all-cause mortality from ICU admission were
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ventilation failure due to discomfort and interface intolerance,
compared to GABA receptor agonists (including pro-
an important approach that can be used to treat non-invasive
Our results suggest that dexmedetomidine-based sedation is
signs and symptoms, including hypoxemia and tachypnea.
Recently, studies using various sedative drug (remifeni-
tani, propofol, midazolam) in patients who became agitated
during NIV demonstrated their efficacy for sedation (15-17).
Midazolam was selected as the medication for comparison in
our study owing to its frequent use for long-term seda-
tion, and it was administered as a continuous infusion owing to its short half-life (18). The Ramsay scale, one of the most
widely adopted sedation scales, is an intuitively obvious scale, and therefore was used to assess the effectiveness of the sedatives in our study because of its facile interpretation.
In the study, all patients treated with dexmedetomidine or
midazolam satisfied the target criteria of a Ramsay score of 2 or more within 1 hour, experiencing adequate sedation even at low initial loading dose. Both groups of patients showed a significant improvement of their cardiorespiratory signs and symptoms, including hypoxemia and tachypnea. Our results suggest that dexmedetomidine-based sedation is an important approach that can be used to treat non-invasive ventilation failure due to discomfort and interface intolerance, compared to GABA receptor agonists (including propofol and benzodiazepines such as midazolam) which have been the most commonly administered medications.
Despite the similar levels of sedation attained by both pa-
patients treated with dexmedetomidine and midazolam, several important differences were noted in this prospective, ran-
domized study. The primary outcome assessed for this investi-
gation, the need for ETI and mechanical ventilation, decreased markedly in dexmedetomidine-treated patients com-
pared with midazolam-treated patients. Furthermore, patients treated with dexmedetomidine were more rapidly weaned from ventilation and had a shorter overall ventilation time, and a lower incidence of pneumonia and vomiting. Each ad-
ditional day of endotracheal intubation and ventilation lead to an increased risk of prolonged hospitalization. Similarly,
infections developing in ICU patients are associated with increased lengths of ICU stay and cost (19, 20), which have already been supported by our observations. Therefore, the desired level of sedation and improved outcome obtained by the effect of dexmedetomidine on NIV treatment improved many important aspects of critical care compared with the conventional sedative.

Based on a further analysis of the causes of ETI, the most common causes related to sedation included vomiting and copious airway secretion. Ideal sedation with less significant respiratory depression and easier arousal would help patients to discharge their secretions and avoid aspiration, ultimately leading to an increase in the rate of NIV success. Dexmedetomidine binds at α2 receptors rather than GABA receptors, and the patients can be aroused easier with adequate sedation and present less significant respiratory depression (21). This may explain the improved outcomes for using dexmedetomidine for patient sedation even when the elements of best sedation practice (including daily arousal, a consistent light-to-moderate sedation level) were used for both groups of patients. However, no significant difference in the cause of the need for ETI between the midazolam and dexmedetomidine groups were observed in our study, likely because of the small number of subjects evaluated.

In the previous studies, it was reported that the initial loading dose of dexmedetomidine may cause cardiovascular adverse drug reactions, such as hypertension, hypotension, or bradycardia (22-24). The results of the present study suggest that dexmedetomidine was associated with an increased incidence of bradycardia compared to midazolam, but this adverse event did not require special intervention or discontinuation of the drug. In addition, there were also no demonstrable differences in hypotension between the patients treated with dexmedetomidine and midazolam. Moreover, no evidence of rebound hypertension or tachycardia was detected during the 48 hour follow-up period after stopping dexmedetomidine. This suggests that when initiated at a low initial loading dose, followed by continuous infusion, dexmedetomidine can provide both adequate sedation and a safer control of sedation in NIV patients.

This study has some limitations that should be kept in mind when interpreting the results. First, this study enrolled few patients, and the cause of ETI could not be effectively analyzed and compared between the midazolam and dexmedetomidine groups. Second, we used only one sedation scoring system. Several other scales, such as the Richmond Agitation Assessment Scale, the Motor Activity Assessment Scale or the Sedation Agitation Scale should be used to ensure that a patient is receiving the optimal dose of a sedative. Third, although midazolam is often identified as the sedative most commonly used for long-term sedation, common alternatives such as lorazepam or propofol were not tested in this study. Fourth, the effect of dexmedetomidine on the cardiovascular system and invasive hemodynamic measurements should be further investigated in patients with acute heart failure.

**Conclusion**

This investigation showed a significant effect of dexmedetomidine on avoiding the failure of non-invasive ventilation in patients with acute cardiogenic pulmonary edema, compared with conventional the sedative drug, midazolam. Despite the similarity in the sedation levels induced by the two drugs, dexmedetomidine was associated with a more desired level of awake sedation, a shortened time to removal from mechanical ventilation, and a reduced length of the ICU stay, as well as a decreased prevalence of nosocomial infections. Although it did not decrease the ICU mortality, dexmedetomidine appears to provide several advantages and safe control for NIV sedation in patients with acute cardiogenic pulmonary edema in comparison to the GABA agonist, midazolam.

**The authors state that they have no Conflict of Interest (COI).**

**References**


