Dexmedetomididine for Sedation During Noninvasive Ventilation in Pediatric Patients

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Objectives: To describe the use of dexmedetomididine for sedation in a large cohort of nonintubated children with acute respiratory insufficiency receiving noninvasive ventilatory support.

Design: Single-center, retrospective, observational cohort study.

Setting: A large quaternary-care PICU.

Patients: The study cohort included 202 children receiving noninvasive ventilatory and a dexmedetomididine infusion within 48 hours of PICU admission over a 6-month period.

Interventions: None.

Measurements and Main Results: The primary respiratory diagnoses in the cohort (median age, 2 yr) included status asthmaticus (60%) and bronchiolitis (29%). Dexmedetomididine was infused for a median of 35 hours with a median hourly dose across the patient cohort of 0.61 μg/kg/hr (range, 0.4–0.8 μg/kg/hr). The target sedation level was achieved in 168 patients (83%) in the cohort for greater than or equal to 80% of the recorded values over the entire noninvasive ventilatory course, with dexmedetomidine as the only continuously administered sedative agent. While vital signs were frequently abnormal relative to age-based norms, clinical interventions were needed rarely to treat bradycardia (13%), hypotension (20%), and hypopnea (5%). The most frequently used of these interventions was a dexmedetomididine dose reduction, fluid bolus, and titration of noninvasive ventilatory support.

Conclusions: Dexmedetomididine was often effective as a single continuous sedative infusion during pediatric noninvasive ventilation. Cardiorespiratory events associated with its use were typically mild and/or reversible with dose reduction, fluid administration, and/or noninvasive ventilatory titration. Prospective studies comparing dexmedetomidine with other agents in this setting are warranted. (Pediatr Crit Care Med 2017; XX:00–00)

Key Words: dexmedetomididine; noninvasive ventilation; sedation

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Over the past 10 years, there has been an increase in the use of noninvasive ventilation (NIV) including biphasic positive pressure ventilation (BiPAP) and continuous positive airway pressure (CPAP) ventilation in children with respiratory insufficiency. This therapy allows for the provision of respiratory support while avoiding endotracheal intubation in many patients. The use of this technique requires the application of a tight-fitting mask and necessitates synchronous breathing with the device. Many pediatric patients, particularly young children, require sedation in order to effectively tolerate this process.

Dexmedetomididine (Precedex, Hospira Worldwide, Lake Forest, IL) is frequently used in our PICU as the first-line agent for sedation in this patient population. Dexmedetomididine is the pharmacologically active dextro-isomer of medetomidine, exerting its physiologic effects via \( \alpha_2 \)-adrenergic receptors (1). Its effects include anxiolysis and sedation with minimal effects on respiratory function and upper airway dynamics (1–6). Although there are published data in the adult population, there are no reports regarding the use of dexmedetomididine for sedation during NIV in pediatric patients (7–9). We therefore designed a single-center, retrospective study to test the hypotheses that 1) dexmedetomidine as a single continuous agent would be sufficient to achieve the target sedation level in the...
majority of children receiving NIV, 2) adverse cardiorespiratory events including bradycardia, hypotension, and respiratory depression will occur infrequently, and 3) these adverse events would have limited clinical implications and be reversible with dose reduction.

METHODS
This retrospective chart review was approved by the Institutional Review Board of Nationwide Children’s Hospital, Columbus, Ohio (IRB13-00334), and was registered at ClinicalTrials.gov. Data were reviewed in the electronic medical record by a single reviewer (R.V.) and were cross-checked by other authors for reliability. All admissions to our 40-bed quaternary care PICU over a 6-month period were screened. Inclusion criteria were PICU admission for respiratory insufficiency and initiation of both NIV and a dexmedetomidine infusion within 48 hours of PICU admission. The definition of NIV included the use of CPAP, BiPAP, or high-flow nasal cannula. Exclusion criteria included age greater than or equal to 18 years, endotracheally intubated patients, patients with a tracheostomy, and patients who were on NIV and dexmedetomidine for less than 3 hours.

Demographic data collected included age, gender, primary diagnosis causing respiratory insufficiency, hospital length of stay (LOS), and PICU LOS. To test the first part of our hypothesis relating to achievement of target sedation score, we collected the following information: starting dose of dexmedetomidine, any dose adjustments, reason for dose adjustment (if known), and the total duration of infusion (hr). We also documented the use of other continuous or intermittent sedative drugs. Data were collected for each patient only for the first 7 days after starting dexmedetomidine. If the duration of the infusion was shorter than 7 days, data were collected until either the dexmedetomidine infusion and/or NIV was discontinued or the patient required endotracheal intubation for respiratory failure. The adequacy of sedation was assessed using the State Behavioral Scale (SBS) (10) (Fig. 1) which is routinely measured in our PICU every 4 hours during continuous sedation, with a typical target SBS score of 0 to –1 while on NIV.

To test the second and third parts of our hypothesis related to adverse cardiorespiratory events associated with dexmedetomidine use, we collected physiologic data including heart rate, blood pressure, and respiratory rate. Bradycardia, hypotension, and hypopnea were defined as values less than the 5th percentile for age as defined by Pediatric Acute Life Support (PALS) criteria (www.cpr.heart.org). The extremes of vital signs were recorded in 4-hour epochs while on dexmedetomidine. Data were also collected on interventions that were performed to manage these events. Clinically significant events in the case of bradycardia and hypotension were defined as those treated with discontinuation or dose reduction of dexmedetomidine, fluid boluses, vasopressors, or cardiopulmonary resuscitation (CPR). Additionally, hypopnea associated with 

Data are expressed as the median with interquartile ranges, as data were nonparametrically distributed. Proportions were expressed in percentages. Data were analyzed using the SAS statistical software (SAS institute, Cary, NC).

RESULTS
Three hundred ninety-six patients received a dexmedetomidine infusion upon admission to the PICU during the study period. Of these, 202 patients met inclusion criteria and were included in the analysis (Fig. 2). Ninety-seven of the 202 patients (48%) were male and 105 (52%) were female. Primary diagnoses necessitating NIV therapy included status asthmaticus (60%), bronchiolitis (29%), or septic shock and other (11%). The demographic characteristics are summarized in Table 1. In 194 of 202 patients (96%), the outcome of the NIV course was weaning from noninvasive respiratory support to nasal cannula or room air within 7 days. Five of 202 patients (2.5%) required endotracheal intubation. Three patients (1.5%) remained on NIV at the end of the 7-day period of data collection.

Dexmedetomidine was infused for a median of 35 hours (17.5–51.5 hr). The minimum duration of the infusion was 4.5 hours and the maximum was 652 hours. The median average hourly dose across the patient cohort was 0.61 μg/kg/hr (0.4–0.8 μg/kg/hr) with a maximum infusion rate of 1.5 μg/kg/hr. One hundred forty of the 202 patients (69%) received dexmedetomidine for more than 24 hours and 74 patients (37% of the total cohort of 202) received dexmedetomidine for more than 48 hours.

Documentation of measured and target sedation scores was present for 2,039 of 2,872 expected observation points (71%) among the cohort as a whole. Eleven patients (5.4%) had no target or actual SBS scores documented. One hundred sixty-eight patients (83% of the full cohort) achieved the target sedation level (SBS, 0 to –1) for at least 80% of recorded values over the entire NIV course. Of these patients, 146 achieved the target sedation level at least 80% of the time with the dexmedetomidine infusion alone. The remaining patients who successfully achieved target sedation level needed at least one dose of an additional agent for sedation, but most were intermittent doses. A minority of patients (7% of the cohort) received additional sedative infusions.

Among the 158 patients for whom documentation of measured and target SBS scores throughout the first 8 hours of dexmedetomidine infusion were available, 101 (64%) achieved the target level of sedation level (SBS, 0 to –1) with dexmedetomidine as a single continuous agent. An additional 24 of the 158 patients were able to achieve the target sedation level within 8 hours with dexmedetomidine and at least one dose of an intermittent sedative agent.

Of the 106 patients (52% of the entire cohort) who received at least one dose of an adjunctive sedative medication at some point during the NIV course, the majority required only one or two doses, whereas 65 patients (32%) required greater than or equal to five doses of additional intermittent sedative agents. Of those patients who required greater than or equal to five doses of an additional agent, 45 (69%) were on the dexmedetomidine infusion for greater than or equal to 48 hours. The most
<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Definition</th>
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| -3    | Unresponsive                         | • No spontaneous respiratory effort  
|       |                                      | • No cough or coughs only with suctioning  
|       |                                      | • No response to noxious stimuli  
|       |                                      | • Unable to pay attention to care provider  
|       |                                      | • Does not distress with any procedure (including noxious)  
|       |                                      | • Does not move  
| -2    | Responsive to noxious stimuli         | • Spontaneous yet supported breathing  
|       |                                      | • Coughs with suctioning/ repositioning  
|       |                                      | • Responds to noxious stimuli  
|       |                                      | • Unable to pay attention to care provider  
|       |                                      | • Will distress with a noxious procedure  
|       |                                      | • Does not move/ occasional movement of extremities or shifting of position  
| -1    | Responsive to gentle touch or voice   | • Spontaneous but ineffective non-supported breaths  
|       |                                      | • Coughs with suctioning/ repositioning  
|       |                                      | • Responds to touch/ voice  
|       |                                      | • Able to pay attention but drifts off after stimulation  
|       |                                      | • Distresses with procedures  
|       |                                      | • Able to calm with comforting touch or voice when stimulus removed  
|       |                                      | • Occasional movement of extremities or shifting of position  
| 0     | Awake and able to calm               | • Spontaneous and effective breathing  
|       |                                      | • Coughs when repositioned/ occasional spontaneous cough  
|       |                                      | • Responds to voice/ no external stimulus is required to elicit response  
|       |                                      | • Spontaneously pays attention to care provider  
|       |                                      | • Distresses with procedures  
|       |                                      | • Able to calm with comforting touch or voice when stimulus removed  
|       |                                      | • Occasional movement of extremities or shifting of position/ increased movement (restless/ squirming)  
| +1    | Restless and difficult to calm       | • Spontaneous effective breathing/ having difficulty breathing with ventilator  
|       |                                      | • Occasional spontaneous cough  
|       |                                      | • Responds to voice/ no external stimulus is required to elicit response  
|       |                                      | • Drifts off/ Spontaneously pays attention to care provider  
|       |                                      | • Intermittently unsafe  
|       |                                      | • Does not consistently calm despite 5 minute attempt/ unable to console  
|       |                                      | • Increased movement (restless/ squirming)  
| +2    | Agitated                             | • May have difficulty breathing with ventilator  
|       |                                      | • Coughing spontaneously  
|       |                                      | • No external stimulus required to elicit response  
|       |                                      | • Spontaneously pays attention to care provider  
|       |                                      | • Unsafe (biting ETT, pulling at lines, cannot be left alone)  
|       |                                      | • Unable to console  
|       |                                      | • Increased movement (restless, squirming or thrashing side-to-side, kicking legs) |

*Figure 1. State Behavioral Scale (SBS) (10). ETT = endotracheal tube.*
common supplemental sedative agent used was IV lorazepam (59%). Other agents used as adjuncts to the dexmedetomidine infusion included IV midazolam (44%) and enteral chloral hydrate (39%). Fourteen subjects (7%) received continuous IV infusions of other sedative/analgesic drugs including IV midazolam (n = 6, 3%) and hydromorphone (n = 5, 2.5%) in addition to dexmedetomidine.

When evaluating vital sign changes relative to age-based norms, bradycardia occurred in 26 patients (13%), hypotension in 56 patients (28%), and hypopnea in 136 patients (67%) at some time during the dexmedetomidine course. After applying the a priori definitions for clinically relevant events, clinically significant bradycardia was seen in 26 patients (13%), clinically significant hypotension in 41 patients (20%), and clinically significant hypopnea in only 11 patients (5%) (Table 2). Among those who received an intervention for an adverse event, the most common was dose reduction or discontinuation of the dexmedetomidine infusion. All 26 patients who met criteria for bradycardia for age received a dexmedetomidine dose reduction or discontinuation as their only intervention. Of the 41 patients who had clinically relevant hypotension, fluid boluses and/or dexmedetomidine dose adjustment were common. The vast majority of hypopnea events did not require clinical intervention. Eleven patients exhibited transient desaturation in the setting of hypopnea that was managed with titration of NIV support. One patient, a 1-month-old infant with bronchiolitis, experienced apnea with progression to bradycardic arrest. This was the only patient in the cohort (1/202 or 0.5%) who received CPR and vasopressor therapy. This patient received fluid boluses, endotracheal intubation, and the dexmedetomidine infusion was discontinued. Four additional patients (2%) underwent endotracheal intubation: three with progression of their respiratory illness (tachypnea and respiratory distress) and one with septic shock (tachycardia with poor perfusion). There were no deaths among the patients in the study.

**DISCUSSION**

Dexmedetomidine is commonly used in our combined medical/surgical PICU as a continuous infusion to provide sedation and anxiolysis in critically ill, spontaneously breathing infants and children with respiratory insufficiency to facilitate tolerance of NIV. This represents the largest report to date of

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Information of the Study Cohort</th>
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<tbody>
<tr>
<td>Demographic Feature</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
</tr>
<tr>
<td>&lt; 6 mo, n (%)</td>
</tr>
<tr>
<td>6 mo to 1 yr, n (%)</td>
</tr>
<tr>
<td>1–2 yr, n (%)</td>
</tr>
<tr>
<td>&gt; 2 yr, n (%)</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
</tr>
<tr>
<td>Status asthmaticus</td>
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<tr>
<td>Acute bronchiolitis</td>
</tr>
<tr>
<td>Malignancy or other oncologic diagnosis</td>
</tr>
<tr>
<td>Croup</td>
</tr>
<tr>
<td>Septic shock</td>
</tr>
<tr>
<td>Admit weight (kg), median (IQR)</td>
</tr>
<tr>
<td>PICU length of stay (d), median (IQR)</td>
</tr>
<tr>
<td>Hospital length of stay (d), median (IQR)</td>
</tr>
<tr>
<td>Cumulative total dose of dexmedetomidine, μg/kg, median (IQR)</td>
</tr>
<tr>
<td>Total hours on dexmedetomidine, median (IQR)</td>
</tr>
<tr>
<td>Total days on dexmedetomidine, median (IQR)</td>
</tr>
</tbody>
</table>

IQR = interquartile range.

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**Figure 2.** Screening and enrollment summary for the study cohort. DEX = dexmedetomidine, NIV = noninvasive ventilatory.
Dexmedetomidine is a selective \( \alpha_2 \)-adrenergic receptor agonist that possesses anxiolytic and sedative properties, with minimal tendency for respiratory depression. Current uses described in the literature include sedation in the intensive care setting, and as an adjunctive agent for procedural sedation and analgesia (1). Its use in the setting of postoperative cardiac surgery has been well described in children, including infants and neonates (11–14). The use of dexmedetomidine was recently reported in a cohort of more than 1,000 intubated children with acute respiratory failure with the conclusion that it works well as a primary sedative agent in those with low criticality and may facilitate tracheal extubation (15).

The therapeutic effects of dexmedetomidine are mediated throughout the central nervous system, with the sedative and anxiolytic effects resulting from its activity in the locus ceruleus and the anxiolytic effects from the dorsal horn of the spinal cord (16). Because of its sympatholytic activity, the most common adverse effects are bradycardia and hypotension. Notable beneficial effects, which may be particularly relevant in the setting of NIV, include its potential to decrease airway reactivity and limit the frequency of delirium in the ICU setting. Groeben et al (17) suggested that dexmedetomidine infusion may have a therapeutic effect in bronchospasm and may decrease airway reactivity, based on the results of their animal study with histamine-induced bronchoconstriction. In addition, dexmedetomidine may be less likely to cause delirium when compared with benzodiazepines such as midazolam and has been shown to not disrupt sleep cycles, facilitating non-rapid eye movement sleep patterns (18, 19).

For these reasons, dexmedetomidine is an attractive agent for use in the spontaneously breathing patient in whom control of agitation without respiratory depression remains a key clinical goal. The literature on the use of dexmedetomidine during NIV is relatively sparse and is limited to adult populations. Case series have demonstrated that dexmedetomidine can safely resolve acute agitation during NIV therapy with limited and reversible adverse effects on hemodynamic function (7, 8). A small prospective study of 10 adult patients using dexmedetomidine during NIV reported that all patients achieved target sedation score within 1 hour of initiation of the infusion without substantial hemodynamic changes (9). Similar results were reported in a subsequent randomized trial of 40 adult patients with acute agitation during NIV therapy (20). Dexmedetomidine and midazolam infusions were equivalent in their ability to maintain patients at the desired level of sedation and maintain hemodynamic stability. A more recent randomized trial of 62 adult patients with cardiogenic pulmonary edema found that sedation with dexmedetomidine during NIV was associated with a lower need for endotracheal intubation, shorter ICU LOS, and shorter time of mechanical ventilation (4).

Despite its popularity and the large clinical experience in the pediatric population, dexmedetomidine has Food and Drug Administration approval only for use in adults for up to 24 hours either for sedation during mechanical ventilation or as an agent for sedation during monitored anesthesia care. The majority of data concerning the pediatric applications of dexmedetomidine remain centered on its use for short durations (< 72 hr) and in endotracheally intubated, mechanically ventilated patients (1, 2, 5, 6, 11–15). We report the use of dexmedetomidine for sedation during NIV in 202 spontaneously breathing, critically ill infants and children with acute respiratory insufficiency. Using moderate-dose dexmedetomidine infusions (median average hourly dose of 0.61 \( \mu g/kg/hr \)), two thirds of the patients (64%) achieved target sedation level with dexmedetomidine as a single continuous agent alone within 8 hours of initiation of the infusion. Eighty-three percent were able to achieve target sedation level with dexmedetomidine as the primary continually infused sedative agent, allowing for the use of intermittent sedatives, usually lorazepam, during the NIV course. As many patients did not receive a bolus dose of dexmedetomidine, one third of the patients in this series required more than five additional doses of adjunctive agents (lorazepam, midazolam, chloral hydrate, or hydromorphone), especially during the first 4–6 hr of therapy with NIV. Most patients (96%) had a successful outcome of the NIV course and were eventually weaned from NIV to nasal cannula or room air with failure of NIV occurring rarely (5/202, 2.5%).

### TABLE 2. Adverse Cardiorespiratory Events During Dexmedetomidine Infusion

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bradycardia</th>
<th>Hypotension</th>
<th>Hypopnea</th>
<th>Cardiorespiratory Arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall frequency</td>
<td>26/202 (13%)</td>
<td>56/202 (28%)</td>
<td>136 (67%)</td>
<td>1/202 (0.5%)</td>
</tr>
<tr>
<td>Event required intervention</td>
<td>26/202 (13%)</td>
<td>41/202 (20%)</td>
<td>11/202 (5%)</td>
<td>1/202 (0.5%)</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine dose reduction</td>
<td>26/202 (13%)</td>
<td>25/202 (12%)</td>
<td>0/202 (0%)</td>
<td>1/202 (0.5%)</td>
</tr>
<tr>
<td>Fluid bolus</td>
<td>0/202 (0%)</td>
<td>32/202 (16%)</td>
<td>0/202 (0%)</td>
<td>1/202 (0.5%)</td>
</tr>
<tr>
<td>Vasoactive drug</td>
<td>0/202 (0%)</td>
<td>0/202 (0%)</td>
<td>0/202 (0%)</td>
<td>1/202 (0.5%)</td>
</tr>
<tr>
<td>Titration of respiratory support</td>
<td>0/202 (0%)</td>
<td>0/202 (0%)</td>
<td>11/202 (5%)</td>
<td>1/202 (0.5%)</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>0/202 (0%)</td>
<td>0/202 (0%)</td>
<td>0/202 (0%)</td>
<td>1/202 (0.5%)</td>
</tr>
</tbody>
</table>

*Sixteen subjects received both dose reduction and fluid bolus.*
Vital sign abnormalities, as defined using PALS criteria, were noted with bradycardia occurring in 13% of subjects, hypotension in 28%, and respiratory depression or hypopnea in 67%. Clinically relevant vital sign changes were rare and typically manageable with dexmedetomidine dose reduction, fluid administration, or titration of NIV. The one patient in the cohort who had apnea and a bradycardic arrest while on dexmedetomidine was a 1-month-old infant with bronchiolitis. Although the apnea episode was felt to be related to the subject’s underlying disease process, it is possible that dexmedetomidine may have been contributory. Eventually, the patient underwent successful tracheal extubation and had a favorable outcome.

The goals of sedation during NIV vary somewhat from those during endotracheal intubation and mechanical ventilation. During NIV, the goals include preservation of the day-night cycle in the hopes of limiting delirium, tolerance of the external device (mask or nasal prongs), and improvement of synchrony with respiratory support. These must be achieved while avoiding deleterious effects on upper airway patency, diaphragmatic function, and central control of ventilation. Given the paucity of evidence-based medicine, there are limited data in the pediatric population demonstrating the superiority of one agent over another (21). In clinical practice, various agents or combinations of agents have been used to provide sedation during NIV including opioids, benzodiazepines, ketamine, and dexmedetomidine. Concerns with an increased frequency of delirium may limit the use of benzodiazepines in this and other clinical scenarios (18, 19). As opioids and benzodiazepines may impact upper airway patency and central control of ventilation, dexmedetomidine and ketamine may be the preferred options (22, 23). Although ketamine has a limited impact on respiratory function at doses used for procedural sedation and may improve respiratory dynamics (decreased airway resistance, improved dynamic compliance, preservation of functional residual capacity), ketamine may increase airway secretions and lead to delirium and emergence reactions (23, 24).

The retrospective nature of the study represents a major limitation. A retrospective analysis likely results in the significant underreporting of physiologic changes, clinical events, and clinician responses. As such, the information provided can only be accepted as preliminary data which must be further studied in prospective trials with head-to-head comparisons with other agents. It is impossible to differentiate the effects of dexmedetomidine from other causes of bradycardia, hypotension, or hypopnea (e.g., the patient’s underlying condition, other medications, or adjunct sedative medications). Our results may not be generalizable to all critically ill children given that we did not include neonatal or cardiothoracic ICU patients. Also, documentation of actual and target sedation scores was unavailable for approximately 30% of the 4-hour epochs included in this study. This limitation is mitigated somewhat by the fact that 95% of subjects did have sedation scoring performed, albeit less consistently than intended. Furthermore, as the protocol for the use of dexmedetomidine was not controlled, there was significant variability in the clinical practice involving the decision to initiate and titrate NIV as well as the choice of agent for sedation. Given the limited variability in our clinical practice, dexmedetomidine is the primary agent used for sedation. However, variability existed with the choice of a supplemental (secondary) agent when adjunctive sedation was needed.

This is the first large-scale report of dexmedetomidine as the primary sedative agent for the specific indication of tolerance of NIV in spontaneously breathing, critically ill infants and children. The outcomes and findings of our study mirror the findings of both the adult and pediatric literature with respect to the hemodynamic side effect profile of dexmedetomidine. The results are encouraging, with most patients successfully completing their NIV course, and a low rate of clinically significant cardiorespiratory adverse events. Seventy-eight of the patients (39%) in the study manifested changes in vital signs that met our thresholds for identification of potential adverse effects. When required, treatment was generally limited to a decrease in the infusion rate or a fluid bolus. As interventions to treat dexmedetomidine-induced vital sign abnormalities were occasionally required, we believe that this supports the need for ICU-level monitoring in this population. As with other sedative agents, tolerance occurs with dexmedetomidine and strategies must be employed for tapering (weaning) the infusion or a transition to other agents (clonidine) following its use for more than 72 hours (25, 26). With these caveats in mind, we noted that dexmedetomidine was effective as the primary continuously administered sedative agent during NIV. Future prospective studies are needed to provide additional information regarding the efficacy and adverse effect profile of dexmedetomidine compared with other commonly used sedative agents such as midazolam.

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