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Original Research

CRITICAL CARE

# Efficacy and Safety of Early Dexmedetomidine During Noninvasive Ventilation for Patients With Acute Respiratory Failure

## A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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***Background:*** **Successful application of noninvasive ventilation (NIV) for acute respiratory failure (ARF) requires patient cooperation and comfort. The efficacy and safety of early IV dexmedetomidine when added to protocolized, as-needed IV midazolam and fentanyl remain unclear.**

***Methods:*** **Adults with ARF and within 8 h of starting NIV were randomized to receive IV dexmedetomidine (0.2 μg/kg/h titrated every 30 min to 0.7 μg/kg/h to maintain a Sedation-Agitation Scale [SAS] score of 3 to 4) or placebo in a double-blind fashion up to 72 h, until NIV was stopped for ≥ 2 h, or until intubation. Patients with agitation (SAS ≥ 5) or pain (visual analog scale ≥ 5 of 10 cm) 15 min after each dexmedetomidine and placebo increase could receive IV midazolam 0.5 to 1.0 mg or IV fentanyl 25 to 50 μg, respectively, at a minimum interval of every 3 h.**

***Results:*** **The dexmedetomidine (n = 16) and placebo (n = 17) groups were similar at baseline. Use of early dexmedetomidine did not improve NIV tolerance (score, 1 of 4; OR, 1.44; 95% CI, 0.44-4.70; *P* = .54) nor, vs placebo, led to a greater median (interquartile range) percent time either tolerating NIV (99% [61%-100%] vs 67% [40%-100%], *P* = .56) or remaining at the desired sedation level (SAS score = 3 or 4, 100% [86%-100%] vs 100% [100%-100%], *P* = .28], or fewer intubations (*P* = .79). Although use of dexmedetomidine was associated with a greater duration of NIV vs placebo (37 [16-72] vs 12 [4-22] h, *P* = .03), the total ventilation duration (NIV + invasive) was similar (3.3 [2-4] days vs 3.8 [2-5] days, *P* = .52). More patients receiving dexmedetomidine had one or more episodes of deep sedation vs placebo (SAS ≤ 2, 25% vs 0%, *P* = .04). Use of midazolam (*P* = .40) and episodes of either severe bradycardia (heart rate ≤ 50 beats/min, *P* = .18) or hypotension (systolic BP ≤ 90 mm Hg, *P* = .64) were similar.**

***Conclusions:*** **Initiating dexmedetomidine soon after NIV initiation in patients with ARF neither improves NIV tolerance nor helps to maintain sedation at a desired goal. Randomized, multicenter trials targeting patients with initial intolerance are needed to further elucidate the role for dexmedetomidine in this population.**

***Trial registry:*** **ClinicalTrials.gov; No: NCT00871624; URL: www.clinicaltrials.gov**

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**Abbreviations:** ARF = acute respiratory failure; IQR = interquartile range; NIV = noninvasive ventilation; SAS = Sedation-Agitation Scale; VAS = visual analog scale

Noninvasive positive-pressure ventilation is increasingly being used to manage patients with acute respiratory failure (ARF)[1,2] in an effort to avoid the negative sequelae associated with intubation.[3] However, noninvasive ventilation (NIV) failure remains a challenging aspect of NIV management, with rates approaching 40% in recent studies.[4,5] Patient intolerance and agitation, often related to mask intolerance

or claustrophobia, are considered frequent contributors to NIV failure.[6-9] Despite data suggesting that use of sedatives (eg, midazolam, propofol) or opioids may improve patient comfort and tolerance during NIV,[10-12] clinicians are hesitant to administer these agents because of concerns that they may induce respiratory depression.[13,14] Moreover, benzodiazepines and opioids are frequently challenging to titrate their pharmacologic effects because they may accumulate after repeated dosing,[15,16] and benzodiazepines are associated with greater delirium.[17]

Dexmedetomidine is a short-acting IV-administered $\alpha_2$ adrenoreceptor agonist that produces a state of cooperative sedation, facilitating patient-caregiver interaction.[18,19] Compared with midazolam and propofol, dexmedetomidine will not affect respiratory drive, has analgesic properties that reduce the need for IV opioid coadministration, has bronchodilator effects, and is less likely to cause delirium.[20-22] Case series have demonstrated that dexmedetomidine will safely resolve acute agitation that occurs during NIV.[23-25] One small, randomized trial of patients with acute agitation while receiving NIV reported that continuous IV dexmedetomidine and midazolam are equivalent in their ability to maintain patients at the desired level of sedation, optimize gas exchange, and maintain hemodynamic stability.[26] In a more recent randomized trial of 62 patients with cardiogenic pulmonary edema refusing to continue NIV due to discomfort, use of infused dexmedetomidine was associated with a lower intubation rate and shorter stays on mechanical ventilation and in the ICU.[27] On the basis of these observations and the favorable pharmacologic profile of dexmedetomidine for use during NIV for ARF, we speculated that compared with as-needed midazolam or fentanyl, routine early use of dexmedetomidine in patients receiving NIV for ARF would be safe, improve NIV tolerance, maintain a more consistent target level of sedation, and avoid NIV failure.

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## Materials and Methods

### *Setting*

This prospective, randomized, double-blind, placebo-controlled study was conducted at two medical centers: Tufts Medical Center, a 320-bed academic medical center in Boston, Massachusetts, and Winchester Hospital, a 200-bed community hospital in Winchester, Massachusetts. The institutional review boards at each institution approved the study (IRB #8533 and IRB #5-2008, respectively), and written informed consent was obtained from all patients prior to randomization.

### *Patients*

From September 2008 to October 2012, consecutive adult patients admitted to an ICU with ARF managed with NIV for ≤ 8 h were evaluated for study participation. Study exclusion criteria were age ≥ 85 years, systolic BP ≤ 90 mm Hg, heart rate ≤ 50 beats/min, the presence of acute decompensated heart failure accompanied by a cardiac ejection fraction ≤ 25%, acute alcohol withdrawal or delirium (Intensive Care Delirium Screening Checklist score ≥ 4),[28] a history of intubation and mechanical ventilation in the past month, heart block without pacemaker use, end-stage liver failure accompanied by encephalopathy, severe dementia, and treatment with clonidine or dexmedetomidine in the past 30 days.[29] At each study site, patients were assigned in blocks of four to one of the two groups in a 1:1 ratio by means of a computer-generated random-number table prepared in advance by the investigational drug service. Treatment allocation was known only to the investigational pharmacist at each site.

### *Study Outcomes*

Tolerance of NIV was evaluated as the main outcome variable using a four-point NIV intolerance score adapted from previously published four- and five-point NIV tolerance scores.[30-32] A score of 1 indicated a comfortable and relaxed patient tolerating NIV; 2, mild intolerance with some discomfort and occasional grabbing at the NIV mask; 3, moderate intolerance and discomfort with the NIV mask most of the time with frequent grabbing at the mask (sometimes pulling it off); and 4, severe NIV intolerance with agitation with an inability to leave the NIV mask in place. This NIV intolerance score was based on the following constructs: (1) degree of NIV intolerance was more important to differentiate in patients than degree of tolerance; (2) specific patient-related descriptors of intolerance (eg, occasional grabbing at the mask) were preferable to general terms like "poor"; and (3) a four-point score was preferable to a five-point score when comparing tolerance scores between two groups. NIV tolerance was evaluated at baseline; after 30 min; after 1, 3, 6, and 12 h of NIV; and thereafter every 12 h until the dexmedetomidine (or placebo) was discontinued. NIV failure was defined as need for intubation or death while NIV was still applied.

The Sedation-Agitation Scale (SAS) score was used to evaluate level of sedation every 4 h, with an SAS score ≥ 5 representing agitation and an SAS score ≤ 2 deep sedation.[33] A 10-cm visual analog scale (VAS) was used to evaluate pain every 6 h, with a score of 0 cm indicating no pain and a score of 10 cm indicating severe pain.[34-36] In situations where the patient was not able to complete the VAS (eg, sedated, visually impaired), the bedside nurse documented the patient's self-reported pain score on the VAS form. Patients were screened for delirium every 12 h using the Intensive Care Delirium Screening Checklist.[28] All sedation, pain, and delirium assessments were conducted by the bedside nurse, who had received prior education regarding each assessment.[37] Hypotension was defined as a systolic BP ≤ 90 mm Hg, bradycardia as a heart rate ≤ 50 beats/min, and bradypnea as a respiratory rate ≤ 12 breaths/min.