Dexmedetomidine for Sedation During Pediatric Noninvasive Ventilation

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BACKGROUND: Noninvasive ventilation (NIV) facilitates management of acute respiratory failure without intubation. Many pediatric patients cannot tolerate the discomfort associated with noninvasive support and require sedation with agents that may decrease respiratory drive. Dexmedetomidine does not decrease respiratory drive, and we hypothesized that its use would increase tolerance of noninvasive respiratory support without increasing risk for intubation. METHODS: A retrospective chart review was performed of all subjects at least 3 months of age with acute respiratory failure requiring NIV who were admitted to the pediatric ICU at a children's hospital for a 3-y period from 2015–2018. Subjects were stratified to those receiving continuous dexmedetomidine versus those not receiving sedation. Medical history was reviewed for developmental delay (DD) or intellectual disability (ID) as well as basic demographic information. To control the association between these variables with both dexmedetomidine use and intubation, augmented inverse probability weighting was utilized to establish equivalent baselines between the dexmedetomidine and no-sedation groups. Primary outcome was intubation rate within 6 h of initiation of dexmedetomidine infusion or NIV. RESULTS: Based on the strong association between age and dexmedetomidine use, a statistical model including subjects > age 5 was not able to be generated, and these subjects were excluded from final analysis. One-hundred eight subjects were included in the final statistical analysis, with 60 receiving dexmedetomidine and 48 receiving no sedation. Dexmedetomidine was effective at reducing agitation, with no difference noted in intubation rate at 6 h between subjects receiving dexmedetomidine versus no sedation (13.1 vs 12.4%). CONCLUSIONS: Dexmedetomidine may allow tolerance of NIV in acute respiratory failure without increasing risk for intubation, especially in preschool age patients and those with DD or ID. A larger study involving multiple centers would help support our conclusions.
Key words: dexmedetomidine; noninvasive ventilation; moderate sedation; hypnotics and sedatives; pediatrics; pediatric ICUs. [Respir Care 2022;67(3):301–307.

Introduction

Noninvasive ventilation (NIV) is the delivery of mechanical respiratory support delivered with a face mask or nasal prongs without the use of endotracheal intubation. Pediatric patients who require NIV respiratory support in the pediatric ICU often appear distressed with the placement of the device on their face and will attempt to remove it. This distress often leads to device displacement or asynchrony with the NIV, rendering it ineffective. In our experience, when CPAP or bi-level positive airway pressure was not tolerated, patients required intubation within a few hours. Sedatives are often required to assist with the patient's ability to tolerate NIV.[1]

Sedation is used to allow tolerance of NIV, but many of the commonly used sedatives depress respiratory drive, decrease oropharyngeal tone, and may cause delirium (especially in younger patients and those with developmental delay [DD]).[2,3] Dexmedetomidine is an alpha$_2$-adrenergic receptor agonist with physiologic effects that include sedation, anxiolysis, and analgesia. Dexmedetomidine has minimal effect on respiratory function, and its sedative properties are similar to natural sleep.[4,5]

Dexmedetomidine has been studied in adult subjects during NIV in the setting of acute respiratory failure, along with protocolized use of intravenous midazolam and fentanyl.[6] Results of this study were that it neither improved NIV tolerance nor helped to maintain sedation at a desired goal. Despite the lack of literature on the safety and efficacy of dexmedetomidine in pediatric subjects, positive outcomes have been anecdotally reported in children's hospitals using dexmedetomidine to decrease agitation and assist with tolerance of NIV.

At the time of onset of the study, dexmedetomidine was on the study institution's formulary for specific indications

but excluded the use for sedation of pediatric patients on NIV. To utilize dexmedetomidine for this indication, a prescriber made a request through the nonformulary medication use process, and a pharmacist evaluated the request on a case-by-case basis.

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The objective of this retrospective cohort study was to evaluate the efficacy of dexmedetomidine to decrease agitation and improve tolerance of NIV for severe respiratory distress. Failure to tolerate NIV was defined as intubation within the first 6 h of dexmedetomidine or NIV initiation. This time period was chosen because it demonstrates an effect of the medication at approximately 3 half-lives, whereas a longer period would be confounded by changes in the patient condition and not a true indicator of sedation effectiveness. We chose to include failure both within 6 h of medication administration or NIV initiation to maximally capture intubation rate in our dexmedetomidine group and to have an appropriate comparator in the control group. Our experience indicated that patients < 3 months did not have the dexterity or strength to interfere with NIV even in absence of sedative medications and would generally not require sedation to tolerate NIV. Aside from this group of infants, we hypothesized that dexmedetomidine use would be skewed toward younger patients and those with developmental or intellectual deficits. Furthermore, we hypothesized that in these patients intubation rates would not increase with use of dexmedetomidine.

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) provides sufficient respiratory support to avoid the need for intubation in many instances. It is poorly tolerated by infants and young children. Commonly used medications such as midazolam allow tolerance of NIV but depress respiratory drive and may further worsen respiratory insufficiency. Dexmedetomidine is an alpha$_2$-adreneric receptor agonist that has sedating qualities with minimal effect on respiratory drive.

What this paper contributes to our knowledge

The use of dexmedetomidine in pediatric subjects allowed tolerance of NIV. This medication was well tolerated as an infusion in children for up to 3 d with predictable side effects that were easily treated with reduction in dose.

Methods

All patients admitted to the pediatric ICU between April 2015–April 2018 of a university children's hospital were included. Approval was granted through our institutional review board. Procedural coding was used to identify subjects requiring NIV, which was defined as continuous or bi-level positive pressure noninvasively. Manual chart review was then performed to determine sedative medications administered, intubation, demographic characteristics, admission diagnosis, and medical history. Subjects were excluded if they were intubated prior to initiation of NIV, if they had do-not-intubate status, intubated electively, or utilized chronic respiratory support at baseline without escalation during admission. Subjects utilizing other sedative medications while supported with NIV were excluded from analysis to avoid confounding.

Basic demographic information was collected from the documentation in the electronic medical record. Subjects were isolated to 3 months of age or older. Medical history for each subject was evaluated for the presence of DD or intellectual disability (ID). Subject encounters were analyzed for duration, timing, and type of NIV. Medication

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The study was performed at Yale-New Haven Children's Hospital, New Haven, Connecticut.

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administration records were examined for type, duration, and timing of sedative medications.

The primary outcome was intubation within the first 6 h after initiation of dexmedetomidine or NIV with a secondary efficacy outcome of intubation rate for the duration of the admission. The maximum duration of dexmedetomidine during NIV was 70 h 55 min. For a comparison group, we used subjects requiring NIV who did not receive sedative medications and evaluated their intubation rates within 6 h of initiation of NIV and for the duration of the admission. We had previously recognized within our population that patients who were younger and/or had DD and were at higher risk for delirium often had escalation of sedation that led to intubation. We, therefore, had a practice of benzodiazepine avoidance and did not have an appropriate comparator group of subjects receiving other sedative agents. A baseline intubation rate of 10% was estimated for subjects with acute respiratory failure requiring NIV, and we chose to evaluate for an increase in intubation rate of 20%. Power calculations estimated a sample size of 124 subjects to provide 80% power with α of 5%.

Significant differences in the dexmedetomidine group were anticipated to be lower age as well as increased presence of DD or ID, both of which may influence the intubation rate. To account for these differences during analysis, augmented inverse probability weighting was utilized to adjust for these confounding factors in the underlying population for the dexmedetomidine versus no-sedation groups. Binomial logistic regression was performed to generate a propensity score for dexmedetomidine based on gender, race-ethnicity, age, and presence of ID or DD. This was then used to assign an augmented inverse probability weight for each subject. Binomial logistic regression was then performed to determine odds of intubation for dexmedetomidine subjects versus no-sedation subjects, with robust standard error from generalized estimating equations. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used to perform these analyses.

Additional secondary outcome measures included a time-to-intubation analysis of all subjects requiring intubation during admission, which was performed using SPSS version 27 (IBM, Armonk, New York). Available sedation scoring was collected as well as safety data to assess for bradycardia and hypotension.

Results

500 patient encounters for NIV were identified, of which 205 met inclusion criteria (Fig. 1). One hundred thirty-seven of these encounters involved subjects who did not require sedation during NIV, with 68 requiring dexmedetomidine (Table 1). The groups were analyzed for difference in age, which was calculated in months, with the no-sedation group averaging 96 months of age (8 y) versus 40 months of age (3 y, 4 months) in the dexmedetomidine group. This difference in age was noted to be significant by Mann-Whitney U test ($P < .001$) (Table 2). Sixty-five of 68 subjects (96%) in the dexmedetomidine group were noted to be 5 y of age (60 months) or younger or to have a diagnosis of DD or ID. In the no-sedation group, 81 of the 137 encounters (59%) were for subjects who met these criteria, with the remaining 56 subjects >5 y of age (> 60 months) and with no documented DD or ID. Whereas the overall distribution of subjects with DD or ID was similar between the 2 groups, the percentage of subjects with DD or ID who were over the age of 5 y was roughly doubled in the dexmedetomidine group (63% vs 37%). Overall, dexmedetomidine was administered to 3 of 64 subjects (4.7%) who were over the age of 5 and without DD or ID versus 5 of 38 subjects (13.5%) > age of 5 with presence of DD or ID.

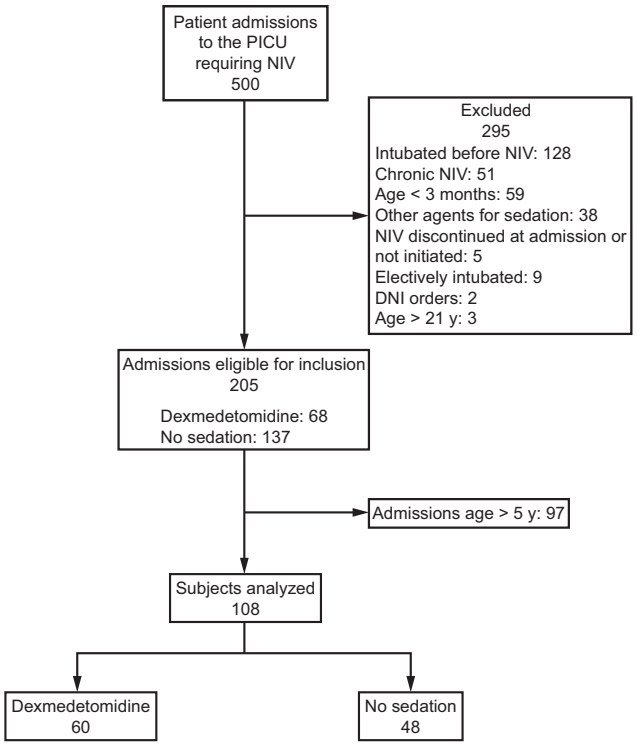

Fig. 1. Flow chart. PICU = pediatric ICU; NIV = noninvasive ventilation; DNI = do not intubate.

Due to the strong association between age and both dexmedetomidine use and intubation, the augmented inverse probability weighting was unable to generate a statistical model that included subjects > age 5 y (60 months). After removing subjects > 60 months of age, 108 subjects were included in the final analysis (60 receiving dexmedetomidine, 48 receiving no sedation), with an excellent covariate distribution between the 2 weighted groups (Fig. 2). There was no statistically significant difference in intubation rates

Table 1. Demographics

	No Sedation	Dexmedetomidine
Subjects	137 (67)	68 (33)
Mean age, months (range)	96 (3–237)	40 (3–193)
Gender		
Female	65 (47)	31 (46)
Male	72 (53)	37 (54)
Race/ethnicity		
White, not Hispanic or Latino	50 (36)	31 (46)
White, Hispanic or Latino	46 (34)	14 (21)
Black or African American	39 (28)	17 (25)
Asian	2 (1)	4 (6)
Multiple races/ethnicities	0	2 (3)
Diagnosis		
Asthma or status asthmaticus	53	17
Bronchiolitis	12	32
Pneumonia	24	4
Viral pneumonia/viral respiratory infection	22	4
Aspiration pneumonia	9	1
Chronic lung disease exacerbation	2	6
Sepsis	2	2
Capillary leak syndrome	2	1
Croup	3	0
Upper airway obstruction	2	0
Acute chest syndrome	1	0
Anaphylaxis	1	0
Apnea	0	1
Atelectasis/splinting	0	1
Cystic fibrosis exacerbation	1	0
Diabetic ketoacidosis	1	0
Heart failure	0	1
Mediastinal mass	1	0
Meningitis	1	0
Metabolic acidosis	0	1
Sinusoidal obstructive syndrome	1	0
Vascular ring	0	1
DD or ID	48 (35)	22 (32)

Data are presented as *n* (%) unless otherwise noted.
DD = developmental delay
ID = intellectual disability

Table 2. Distribution of Subjects in Dexmedetomidine Versus No-Sedation Groups

	Total Number of Subject Encounters	Number of Encounters with ID/DD* or < 5 y of Age	Average Age, mo
Dexmedetomidine	68	65	40, $P < .001$
No sedation	137	81	96, $P < .001$

*ID = intellectual disability
DD = developmental delay

between these groups: 13.09% (95% CI 4.42–27.59) dexmedetomidine versus 12.41% (95% CI 2.68–27.89) no sedation (Table 3), though the 95% CI was wide and included a range of outcomes (Fig. 3).

For our secondary outcome of intubation rates through the duration of hospital admission, there was again no significant difference between the group receiving dexmedetomidine and that receiving no sedation. There was a statistically insignificant trend toward increased intubation rate in the dexmedetomidine group: 28.16% (95% CI 17.75–42.12) versus 19.86% (95% CI 6.63–36.45) (Table 4).

A Kaplan-Meier plot survival analysis indicated an average time on NIV prior to intubation of 1,019.40 (573.15–1,501.65) min in the dexmedetomidine group compared to 690.15 (108.30–1,272.01) min in the no-sedation group (Table 5, Fig. 4).

All 68 subjects who received dexmedetomidine were included in the assessment of safety and efficacy of the medication. Richmond Agitation-Sedation Scale (RASS) or State Behavioral Scale (SBS) scoring was not consistently documented in our retrospective study, with 31 of the 68 subjects who received dexmedetomidine in our study having documented sedation scoring and only 15 using RASS. Subjects were most frequently in the SBS or RASS range 0 to −1, with higher scores responding to increased doses of sedation. Higher scores 2–3 were noted at initiation of dexmedetomidine but rare afterward. Most subjects required dosing in the 0.2–1 μg/kg/h range, with 1 subject requiring a dose as high as 1.2 μg/kg/h and none exceeding this dose. Ten subjects experienced bradycardia while on dexmedetomidine infusion, with the maximum dose ranging from 0.5–1.2 μg/kg/h, and all were noted either to have corresponding dose reductions with improvement in heart rate or their bradycardia was transient and improved spontaneously. No significant events were documented in the medical record relating to bradycardia. Eight subjects experienced hypotension during dexmedetomidine infusion, though this was generally attributed to other causes. Five of these subjects were asthmatics, all of whom were receiving inhaled β_2-agonist therapy, and some received intravenous magnesium sulfate; one was admitted with heart failure in the setting of decreased ventricular function; one was admitted with hypotension in the setting of sepsis, and one had a normal blood pressure documented on repeat 6 min later, indicating a likely measurement error.

Discussion

Dexmedetomidine is approved for use as an infusion for up to 24 h in adults. There are no currently approved indications for children, but it may be an efficacious sedation agent for children receiving NIV for a viral upper respiratory tract infection or asthma exacerbation. Dexmedetomidine is the preferred sedative agent in this setting due to the lack of

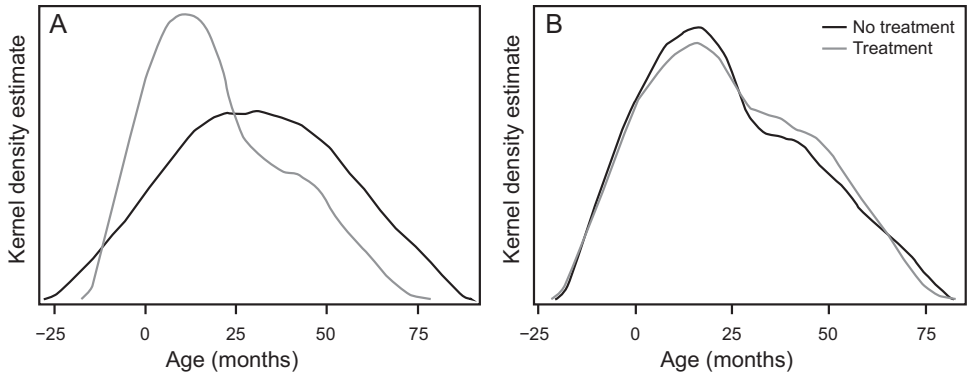

Fig. 2. Distribution of subject age in unweighted sample (A) versus weighted (B) with augmented inverse probability weighting. Negative values represent theoretical extrapolation of the statistical model; all actual subject ages are in range of 3–60 months.

Table 3. Intubation Rate at Less Than 6 Hours

	Intubation Rate, %	95% CI
Dexmedetomidine	13.09	4.42–27.59
No sedation	12.41	2.68–27.89
Average treatment effect	0.68	−16.61 to 18.60

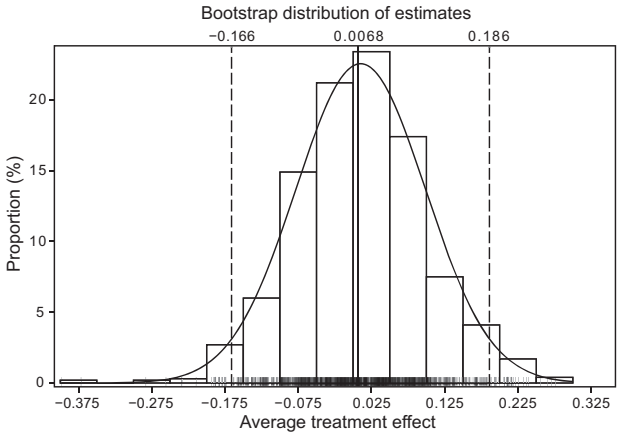

Fig. 3. Distribution of average treatment effect (increase in intubation rate within 6 h) of dexmedetomidine. Treatment effect of one equals an increase of 100%. Vertical line at center denotes the original sample estimate; dashed lines show bias corrected 95% CI.

Table 4. Intubation Rate During Admission

	Intubation Rate, %	95% CI
Dexmedetomidine	28.16	17.75–42.12
No sedation	19.86	6.63–36.45
Average treatment effect	8.30	−12.33 to 28.76

Table 5. Mean Time on Noninvasive Ventilation Prior to Intubation

Dexmedetomidine	Mean Time, min	95% CI	
		Lower Bound	Upper Bound
No	690.15	108.30	1,272.01
Yes	1,019.40	537.15	1,501.65
Overall	866.54	494.65	1,238.42

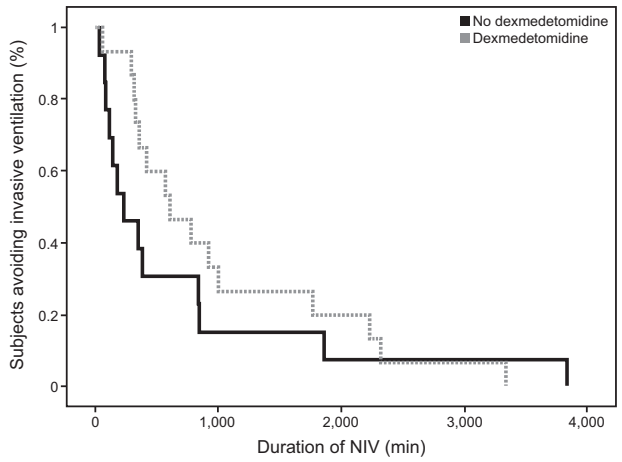

Fig. 4. Time surviving on noninvasive ventilation (NIV) prior to intubation for all subjects requiring intubation at any point during admission.

respiratory depression.[7] Evaluation of sedation quality is limited in our study due to inconsistent sedation scoring, but others have previously demonstrated dexmedetomidine as a successful sedation agent in pediatric subjects requiring NIV.[8,9] Dexmedetomidine may also decrease the paradoxical agitation and delirium associated with midazolam use in the pediatric ICU.[7]

A previous study reported good hemodynamic stability in critically ill children with acquired or congenital heart disease during dexmedetomidine infusions lasting > 24 h. The use of dexmedetomidine facilitated the transition from NIV to high-flow nasal cannula in their subjects.[10] Carroll et al[11] studied dexmedetomidine use for sedation in 60

children, administered 74 times. One of the major indications was to provide sedation for spontaneously breathing children without respiratory depression. Hypotension, hypertension, and bradycardia were identified in 9%, 8%, and 3% of cases, respectively, in that study. These side effects were treated with reducing or stopping the infusion, and none of the subjects required intubation due to dexmedetomidine side effects. Venkatraman et al[1] reported the use of dexmedetomidine for sedation during NIV in pediatric subjects, and they also found that clinical interventions were rarely required to treat bradycardia, hypotension, and hypopnea. The most reported clinical interventions were either a decrease or discontinuation of the dexmedetomidine infusion. One subject (0.5%) required endotracheal intubation due to apnea. Recently, Shutes et al[12] investigated effects of dexmedetomidine as a single continuous agent, identifying bradycardia (75% of subjects) and hypotension (33%) during the escalation of dosing and withdrawal as primarily associated with longer duration of therapy and not significantly associated with peak dose. Our subjects demonstrated infrequent bradycardia that improved with dose reduction and hypotension that was attributable to other underlying conditions or interventions. This analysis was limited by the lack of continuous monitoring data available in retrospective chart review.

Our subjects were on dexmedetomidine for a maximum duration of 70 h 55 min. Whalen et al[13] defined long-term dexmedetomidine use as $>$ 72 h in duration. They reported that 30% of subjects experienced withdrawal symptoms, including tremor, decreased sleep, and agitation. Reports of these symptoms in our subjects were not noted, but we did not prospectively use a validated means of assessment since our infusions were $<$ 5 d.[14] Our study supports the use of dexmedetomidine to decrease agitation during NIV without increasing intubation rate when used for $<$ 72 h.

To our knowledge, whereas there have been studies evaluating side effect profile and effectiveness of sedation with dexmedetomidine, there has not been a significant study comparing failure of NIV in patients receiving dexmedetomidine versus those not receiving pharmacologic sedation. Additionally, many previous studies have not evaluated dexmedetomidine as a single agent for sedation in NIV. Finally, previous studies have examined dexmedetomidine in subjects with high incidence of asthma, which has a relatively low intubation risk for patients requiring NIV. Our subjects in the dexmedetomidine group and the comparison group for intubation had higher rates of bronchiolitis and pneumonia than in prior studies, and the higher rates of intubation in patients with these pathologies may provide more insight on the ability of dexmedetomidine to aid in preventing intubation.

In examining the time to intubation, there is a trend toward longer time spent on NIV in the dexmedetomidine group. The 95% CI for these values overlap, so they do not represent values of statistical significance but may demonstrate that the dexmedetomidine group did not have increased risk for earlier intubation. Our primary outcome was examining intubation within 6 h to broadly capture the possibility for increased intubation in the dexmedetomidine group, but subjects toward the latter half of these 6 h may trend toward changes in underlying disease status rather than effects of sedation.

A limitation of this study is the retrospective cohort design, despite using augmented inverse weighted probability analysis to correct for bias. Sedation scoring was not available for many subjects and limited our ability to determine sedation efficacy with dexmedetomidine. We additionally chose not to compare dexmedetomidine directly to other sedative agents, largely based on the lack of consistent use of other sedative agents at our institution, even prior to increased utilization of dexmedetomidine. Therefore, this study is limited in its ability to draw conclusions on superiority or inferiority of dexmedetomidine in comparison to other pharmacologic sedation. Finally, whereas safety data including heart rate and blood pressure were examined retrospectively, data from continuous monitoring were not available, and only charted vital signs were included.

Conclusions

Dexmedetomidine has been demonstrated to be an efficacious sedative agent to treat agitation and may assist with tolerance of NIV for patients who otherwise would require intubation. Continuous infusion of dexmedetomidine is well tolerated with dose-related effects that easily reverse when the dose is reduced. Patients requiring sedation to tolerate NIV appear to be younger, and patients $>$ 5 y of age who require sedation often have DD or ID. In our pediatric ICU, we found that subjects age 3 months to 5 y were able to tolerate NIV with the use of dexmedetomidine without significantly increasing risk of intubation. Further analysis from a larger patient population and multiple centers, utilizing a standardized scoring tool for level of sedation, would help support this conclusion of improved comfort and patient experience with NIV through utilization of dexmedetomidine.

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