Dexmedetomidine: A Means to an End or Just Delaying the Inevitable?

Noninvasive ventilation (NIV), which includes both bi-level positive airway pressure (BPAP) and CPAP, is one of the most successful and widely used interventions in respiratory care.[1] Beneficial physiologic effects of NIV include restoration of end-expiratory lung volume, unloading of the respiratory muscles through augmented tidal volume and change in diaphragmatic stretch, delivery of controlled and more predictable F_{IO_2}, and improved aerosol deposition in patients receiving nebulized treatments.[1,2] In addition, cardiovascular benefits of NIV include a lower energy consumption from respiratory muscle work and a decrease in left-ventricular afterload.[3] In adult patients, high-level evidence supports the use of NIV for COPD and cardiogenic pulmonary edema.[4,5] In patients with hypercapnia without COPD, NIV reduces the need for intubation compared to standard oxygen therapy, with similar efficacy between BPAP and CPAP.[6] The evidence supporting the use of NIV in acute hypoxemic respiratory failure is less robust, but it has been shown to reduce the need for intubation in immunocompromised patients.[7] NIV has also been shown to be an effective strategy to prevent re-intubation, with the greatest effect observed in high-risk patients.[8] In neonates, NIV is effective at preventing intubation in the delivery room[9] and decreasing the need for re-intubation for those with respiratory distress syndrome.[10]

Evidence for NIV in children is less abundant and of lower quality, suggesting NIV reduces the need for intubation in patients with lower-airway respiratory infection without impacting mortality.[7] Among children, NIV has been most commonly studied in patients with bronchiolitis. However, NIV is also used in the treatment of patients with neuromuscular disease, cystic fibrosis, asthma, ARDS, and as a prophylactic support modality following extubation.[11-15] NIV use in bronchiolitis has increased over the past decade without a concomitant decrease in the need for invasive ventilation, and centers with high rates of NIV utilization also have higher rates of cardiac arrest.[16] In asthma, NIV use has increased over time, although definitive evidence of its impact on the need for invasive mechanical ventilation is lacking.[12] The use of NIV in children with respiratory failure post-hematopoietic cell transplant is associated with an intubation rate of 63%,[11] and when applied to a general population of children with ARDS, it has been associated with worse clinical outcomes.[15]

See the Original Study on Page 301

In clinical practice, intolerance of NIV is a common challenge, especially among younger children or those with intellectual disabilities. The inability to tolerate NIV is usually multifactorial and may be caused by discomfort, agitation, air hunger, suboptimal interfaces, and patient-ventilator asynchrony, among other issues.[17] Generally, when these challenges arise, steps are taken to optimize the patient-device interface and settings. In addition, provision of sedation might be necessary to improve comfort, reduce agitation, or both. This could lead to unintended consequences, as certain types of sedation might adversely affect a child's ability to trigger the ventilator. Difficulty triggering is common, especially in infants, as devices typically used for NIV are not specially designed for children.[17] Due to ineffective triggering, a rate is often set, which can in turn exacerbate patient-ventilator asynchrony. Nasal interfaces that are used preferentially in infants can pose additional challenges due to the occurrence of leaks around the mask or from mouth opening, which can also adversely affect triggering.[17] Full-face masks can be used in infants and small children, although oronasal mask options are limited. Settings can be titrated by increasing CPAP, transitioning to BPAP, and adjusting settings to decrease work of breathing and optimize tidal volume.

Despite optimization of settings, interface, and machine, some patients may still require sedation to facilitate NIV. Most sedatives suppress respiratory drive and are associated with an increased risk of delirium.[18] The ideal sedative would decrease agitation, provide anxiolysis, provide analgesia without affecting respiratory drive or airway reflexes, have a short onset of action, and have a short half-life to allow rapid titration. Dexmedetomidine is a selective, central alpha$_2$-adrenergic receptor agonist with a half-life of 2–3 h in infants and children.[19] It causes a decreased response to endogenous catecholamines, resulting in a

Mr Miller is a Section Editor for Respiratory Care. Dr Heath has disclosed no conflicts of interest. Dr Rotta discloses relationships with Breas US, Vapotherm, and Elsevier.

Correspondence: Andrew G Miller MSc RRT RRT-ACCS RRT-NPS FAARC, 2301 Erwin Rd, Durham, NC 27710. E-mail: Andrew.g.miller@duke.edu.

DOI: 10.4187/respcare.09954

sedated state that is similar to sleep, along with decreased blood pressure and heart rate. Whereas very high doses of dexmedetomidine can decrease the respiratory drive, this does not occur at clinically relevant doses.[20] Its use during NIV in adults has been shown to decrease the need for intubation, reduce the incidence of delirium, and decrease ICU length of stay, without a difference in duration of NIV or mortality; however, it also carries an increased incidence of hemodynamic adverse effects.[21] Its use in children for this indication has been described in several single-center case series.[22-24]

In this issue of RESPIRATORY CARE, Eidman et al[25] report on the use of dexmedetomidine for sedation in children receiving NIV at a single center. They retrospectively reviewed the records of 205 subjects who received NIV, with 68 (33%) receiving dexmedetomidine. They excluded infants ≤ 3 months of age as they felt these children generally tolerate NIV without sedation. They estimated 124 subjects would be needed to detect a 20% increase in intubation rate. To account for the expected differences in baseline characteristics, the authors used inverse probability weighting followed by binomial logistic regression analysis to determine the chances of intubation in each group. Because the rate of dexmedetomidine use was low in children > 5 y of age without disabilities, they were excluded from their statistical model, thus resulting in excellent balancing of covariates. They hypothesized sedation would result in decreased agitation and improved NIV tolerance.

Subjects who received dexmedetomidine were younger than those treated without sedation (mean age 3.3 vs 8.0 y, respectively) and most commonly received NIV for bronchiolitis or asthma. Nearly three-quarters of subjects with bronchiolitis and about a quarter of subjects with asthma received dexmedetomidine. For those with developmental delay, 31% received sedation; and 96% of subjects receiving dexmedetomidine were either < 5 y of age, developmentally delayed, or intellectually disabled. There was no difference in intubation rate between children treated with dexmedetomidine and those who were not treated at 6 h after initiation of NIV or at any point in the hospital stay. For those requiring intubation, there was no statistical difference between the 2 groups in time to intubation; however, the absolute time was 5.5 h longer in the dexmedetomidine group. As expected, higher doses of dexmedetomidine were associated with deeper sedation levels, with most subjects receiving 0.2–1.0 μg/kg/h of dexmedetomidine, and no serious adverse events were recorded in the medical record. Eight subjects experienced hypotension, although the authors attributed these to other causes, primarily intravenous magnesium administration in children with critical asthma. The evaluation of sedation level was limited by inconsistent documentation of sedation scores in their cohort.

Eidman et al[25] should be applauded for sharing their experience, even in light of the multiple limitations in this report. Despite a power analysis, the study was significantly underpowered to detect differences in outcomes as they almost certainly overestimated the potential effect of dexmedetomidine on intubation rate. To detect a 10% decrease in intubation rate, we calculated a sample size of 554 would be required based on their reported 28% failure rate in the dexmedetomidine group. The retrospective nature of the study is a major limitation as it is extremely difficult to retrospectively capture all drug-related adverse events, especially if minor or transient, and try to establish a precise correlation between events and treatment. In addition, the lack of gas exchange data or vital signs before and after NIV initiation in this report significantly diminishes the reader's ability to fully understand the clinical trajectory of subjects in each of the groups. If one were to assume that subjects who received dexmedetomidine were in fact those less likely to have tolerated NIV, it would be reasonable to think these subjects would have had a higher risk of needing intubation. Given the rate of intubation in the group treated with dexmedetomidine was similar to those without sedation, it is possible that NIV tolerance was indeed improved and that sedation may have contributed to NIV success. However, the fact that only 31 of 68 sedated subjects had sedation scores (Richmond Agitation-Sedation Scale or State Behavioral Scale) available for analysis makes it difficult to assess the efficacy and adequacy of dexmedetomidine dosing and the resulting level of sedation. It was also unclear in this report if dexmedetomidine was started due to agitation after NIV initiation or prior to NIV initiation. Furthermore, the availability of dexmedetomidine due to the described institutional restrictions could have posed an additional selection bias. Lastly, this cohort included a large number of subjects with bronchiolitis, a disease process with conflicting data on the utility of NIV to prevent the need for invasive mechanical ventilation.[26-28]

Without granular data on gas exchange, type of NIV device and interfaces used, adequacy and depth of sedation, or a measure of illness severity, it is difficult to determine whether dexmedetomidine was in fact beneficial or to identify which patients may benefit from it, if any. Future studies addressing this topic (or other respiratory support modalities) would benefit from the inclusion of respiratory therapists as part of the investigational team, as their clinical expertise could help identify factors associated with NIV success or failure that a less diverse team may miss. As it stands, it is reasonable to consider having dexmedetomidine readily available at the bedside when initiating NIV in patients with agitation, known intolerance to NIV, or who fall into a "high risk of NIV failure" category such as those with ARDS, multi-organ system failure, or significant respiratory acidosis. It is important to remember that

whereas sedation may reduce agitation related to NIV tolerance or dyspnea it will not ameliorate the underlying pathology (eg, asthma, bronchiolitis, pediatric ARDS) causing respiratory failure and may in fact mask its declining trajectory. Whereas the decision to intubate a child undergoing NIV often is a difficult and complex one, the inability to decrease F_{IO_2} to < 0.6 after initiation of NIV, the presence of persistent respiratory acidosis, or significantly increased work of breathing despite sedation and NIV optimization should prompt intubation without delay to avoid untoward outcomes, especially in patients with ARDS or acute hypoxemic respiratory failure.[29,30]

As discussed by the authors, future studies should focus on a large multi-center prospective randomized controlled trial (RCT) evaluating the utility of dexmedetomidine to improve tolerance of NIV in young children. In contrast to adults, we also require additional RCTs to better elucidate the role of NIV in pediatric acute respiratory failure. Multicenter registry studies may also provide additional evidence in support of sedation to facilitate NIV, but these data sets obtained during the delivery of care can only establish associations, not causation. Future studies should also report more detailed data, including illness severity score, gas exchange data, vital signs, NIV devices used along with their interfaces, and agitation/sedation scores. What is less clear is whether RCTs should be designed to evaluate the use of dexmedetomidine in a diverse cohort of patients receiving NIV or in more homogeneous samples, such as single-disease states (eg, bronchiolitis, asthma) or targeted age or patient subgroups.

Andrew G Miller
Travis Heath
Alexandre T Rotta
Duke University Medical Center
Durham, North Carolina

REFERENCES

1. Hess DR. Evidence-based respiratory care. Respir Care 2021;66 (7):1105-1119.
2. Hess DR. Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. Respir Care 2015;60(6):880-891; discussion 891–883.
3. Pinsky MR. Cardiopulmonary interactions: physiologic basis and clinical applications. Ann Am Thorac Soc 2018;15(Suppl 1):S45-S48.
4. Berbenetz N, Wang Y, Brown J, Godfrey C, Ahmad M, Vital FM, et al. Noninvasive positive-pressure ventilation (CPAP or bi-level NPPV) for cardiogenic pulmonary edema. Cochrane Database Syst Rev 2019;4:CD005351.
5. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Noninvasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;7:CD004104.
6. Faqihi BM, Trethewey SP, Morlet J, Parekh D, Turner AM. Bilevel positive airway pressure ventilation for non-COPD acute hypercapnic respiratory failure patients: a systematic review and meta-analysis. Ann Thorac Med 2021;16(4):306-322.
7. David-Joao PG, Guedes MH, Rea-Neto A, Chaiben VBO, Baena CP. Noninvasive ventilation in acute hypoxemic respiratory failure: a systematic review and meta-analysis. J Crit Care 2019;49:84-91.
8. Sang L, Nong L, Zheng Y, Xu Y, Chen S, Zhang Y, et al. Effect of high-flow nasal cannula versus conventional oxygen therapy and noninvasive ventilation for preventing reintubation: a Bayesian network meta-analysis and systematic review. J Thorac Dis 2020;12(7):3725-3736.
9. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Noninvasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980.
10. Solevag AL, Cheung PY, Schmolzer GM. Bi-level noninvasive ventilation in neonatal respiratory distress syndrome. A systematic review and meta-analysis. Neonatology 2021;118(3):264-273.
11. Rowan CM, Fitzgerald JC, Agulnik A, Zinter MS, Sharron MP, Slaven JE, et al. Risk factors for noninvasive ventilation failure in children post-hematopoietic Cell Transplant. Front Oncol 2021;11:653607.
12. Basnet S, Mander G, Andoh J, Klaska H, Verhulst S, Koirala J. Safety, efficacy, and tolerability of early initiation of noninvasive positive-pressure ventilation in pediatric patients admitted with status asthmaticus: a pilot study. Pediatr Crit Care Med 2012;13 (4):393-398.
13. Gupta P, Kuperstock JE, Hashmi S, Arnolde V, Gossett JM, Prodhan P, et al. Efficacy and predictors of success of noninvasive ventilation for prevention of extubation failure in critically ill children with heart disease. Pediatr Cardiol 2013;34(4):964-977.
14. Punn D, Gill KS, Bhargava S, Pooni PA. Clinical profile and outcome of children requiring noninvasive ventilation (NIV). Indian Journal of Pediatrics 2021.
15. Kopp W, Gedeit RG, Asaro LA, McLaughlin GE, Wypij D, Curley MAQ. The impact of pre-intubation noninvasive ventilation on outcomes in pediatric acute respiratory distress syndrome. Crit Care Med 2021;49(5):816-827.
16. Shanahan KH, Monuteaux MC, Nagler J, Bachur RG. Noninvasive ventilation and outcomes in bronchiolitis. Crit Care Med 2021;49(12): e1234-e1240.
17. Fedor KL. Noninvasive respiratory support in infants and children. Respir Care 2017;62(6):699-717.
18. Mody K, Kaur S, Mauer EA, Gerber LM, Greenwald BM, Silver G, et al. Benzodiazepines and development of delirium in critically ill children: estimating the causal Effect. Crit Care Med 2018;46 (9):1486-1491.
19. Greenberg RG, Wu H, Laughon M, Capparelli E, Rowe S, Zimmerman KO, et al. Population pharmacokinetics of dexmedetomidine in infants. J Clin Pharmacol 2017;57(9):1174-1182.
20. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 2007;8(2):115-131.
21. Lewis K, Piticaru J, Chaudhuri D, Basmaji J, Fan E, Moller MH, et al. Safety and efficacy of dexmedetomidine in acutely ill adults requiring noninvasive ventilation: a systematic review and meta-analysis of randomized trials. Chest 2021;159(6):2274-2288.
22. Piastra M, Pizza A, Gaddi S, Luca E, Genovese O, Picconi E, et al. Dexmedetomidine is effective and safe during NIV in infants and young children with acute respiratory failure. BMC Pediatr 2018;18 (1):282.
23. Venkatraman R, Hungerford JL, Hall MW, Moore-Clingenpeel M, Tobias JD. Dexmedetomidine for sedation during noninvasive ventilation in pediatric patients. Pediatr Crit Care Med 2017;18(9):831-837.
24. Shutes BL, Gee SW, Sargel CL, Fink KA, Tobias JD. Dexmedetomidine as single continuous sedative during noninvasive ventilation: typical usage, hemodynamic effects, and withdrawal. Pediatr Crit Care Med 2018;19(4):287-297.

25. Eidman D, Clauss C, Kelly S, Rhieu J, McCollum S, Couloures K. Dexmedetomidine for sedation during pediatric noninvasive ventilation. Respir Care 2022;67(3)301-307.
26. Delacroix E, Millet A, Pin I, Mortamet G. Use of bi-level positive-pressure ventilation in patients with bronchiolitis. Pediatr Pulmonol 2020;55(11):3134-3138.
27. Clayton JA, McKee B, Slain KN, Rotta AT, Shein SL. Outcomes of children with bronchiolitis treated with high-flow nasal cannula or noninvasive positive-pressure ventilation. Pediatr Crit Care Med 2019;20(2):128-135.
28. Maamari M, Nino G, Bost J, Cheng Y, Sochet A, Sharron M. Predicting failure of noninvasive ventilation with RAM cannula in bronchiolitis. J Intensive Care Med 2022;37(1):120-127.
29. Zeng JS, Qian SY, Wong JJ, Ong JS, Gan CS, Anantasit N, et al. Noninvasive ventilation in children with pediatric acute respiratory distress syndrome. Ann Acad Med Singap 2019;48(7):224-232.
30. Grieco DL, Maggiore SM, Roca O, Spinelli E, Patel BK, Thille AW, et al. Noninvasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. Intensive Care Med 2021;47(8):851-866.