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Review Article

The Role of Dexmedetomidine for Sedation in Critically Ill Adults

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Abstract

Management of pain, agitation, and delirium in mechanically ventilated patients is one of the foundations of therapy in the intensive care unit (ICU). Dexmedetomidine is a selective, centrally-acting α2 adrenergic receptor agonist with sedative, analgesic, and anxiolytic properties. Pertinent literature regarding the safety and efficacy of dexmedetomidine in mechanically (invasive and non-invasive) ventilated ICU patients is reported. In the mixed medical-surgical population, dexmedetomidine is an appropriate sedative to maintain mild to moderate sedation and has been associated with shorter durations of mechanical ventilation and decreased delirium prevalence vs. benzodiazepine-based sedation. In the post-operative cardiac surgery population, dexmedetomidine may decrease the incidence and/or duration of post-operative delirium as compared to other sedation strategies. More well-designed clinical trials are needed to determine dexmedetomidine efficacy and safety in other ICU populations (i.e. neurocritical care). Preliminary data indicates dexmedetomidine can be safely utilized to facilitate non-invasive ventilation in patients intolerant to such therapy and may be associated with improved clinical outcomes. Bradycardia is the most common reported adverse effect but has not been associated with increased interventions.

ABBREVIATIONS

APACHE: Acute Physiology and Chronic Health Evaluation; BiPAP: Bilevel Positive Airway Pressure; CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; CNS: Central Nervous System; COPD: Chronic Obstructive Pulmonary Disease; DSM-IV TR: Diagnostic and Statistical Manual of Mental Disorders; FDA: Food and Drug Administration; ICU: Intensive Care Unit; LOS: Length of Stay; MAAS: Motor Activity Assessment Scale; NIV: Noninvasive Ventilation; PAD: Pain Agitation Delirium; POD: Post-Operative Delirium; RASS: Richmond Agitation-Sedation Scale; RSS: Ramsay Sedation Scale; SAS: Sedation Agitation Scale; SOFA: Sequential Organ Failure Assessment; TBI: Traumatic Brain Injury

INTRODUCTION

Management of pain, agitation, and delirium in mechanically ventilated patients is one of the foundations of therapy in the intensive care unit (ICU). Clinical adverse effects are associated with anxiety and agitation, which occur frequently in this population [1,2]. There are few sedative agents available to manage agitation and anxiety and the risks and benefits of each should be evaluated prior to initiation. An ideal sedative regimen should safely facilitate mechanical ventilation while also reducing the duration for which such support is needed, in addition to ICU length of stay, with minimal adverse effects [3]. Improved patient outcomes have been demonstrated in the literature by providing a light sedation strategy [4-7]. The Pain, Agitation, and Delirium (PAD) Guidelines suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines to improve clinical outcomes in mechanically ventilated adult ICU patients [4].

Dexmedetomidine is a selective, centrally-acting α2 adrenergic receptor agonist with sedative, analgesic, and anxiolytic properties primarily through activity at the locus ceruleus and spinal cord [8-11]. The Food and Drug Administration (FDA) approved indications for dexmedetomidine include sedation of mechanically ventilated ICU patients (0.2 – 0.7 mcg/kg/hr) for a maximum duration of 24 hours, and sedation of non-incubated patients prior to and/or during surgical and other procedures (0.2 – 1 mcg/kg/hr) [8]. Literature exists supporting use of dexmedetomidine for facilitating mechanical ventilation of durations longer than 24 hours and at doses up to 1.5 mcg/kg/hr [12-14] in addition, there are also studies examining use for facilitating noninvasive ventilation (NIV) [15-18]. Overall, dexmedetomidine offers a unique mechanism of action compared to other options such as benzodiazepines, which allows patients to be more arousable with minimal risk for respiratory depression [4,11].

The purpose of this review is to provide a summary of the available data examining the use of dexmedetomidine in adult critically ill patients managed with NIV and invasive mechanical ventilation. We used MEDLINE to search for publications through June 2017 and selected original research articles involving critically ill adult patients. Thereafter, a manual review of each

identified article and their respective references were performed to extract and summarize the most relevant data.

INVASIVE MECHANICAL VENTILATION

Mixed medical-surgical populations

There have been four large, randomized, controlled clinical trials that have evaluated the use of dexmedetomidine for mild to moderate sedation versus other sedative agents (benzodiazepines and/or propofol) (Table 1) [12-14]. The first of these trials was a prospective, double-blind, multicenter, randomized controlled trial of 103 mechanically ventilated patients in medical and surgical ICUs [12]. Pandharipande and colleagues evaluated the effects of dexmedetomidine or lorazepam for continuous sedation up to 120 hours on the composite primary outcome of days alive without delirium or coma. Delirium was assessed by the Confusion Assessment Method for the ICU (CAM-ICU) and coma was defined as a Richmond Agitation-Sedation Scale (RASS) of -4 to -5. The majority of patients in both groups were medical admissions (~70%) with similar median Acute Physiology and Chronic Health Evaluation (APACHE) II scores at baseline ~28. Patients that received dexmedetomidine had more days alive without delirium or coma (median, 7 days vs. 3 days; p = 0.01), which was heavily influenced by overall days alive without coma (median, 10 days vs. 8 days; p < 0.001). Patients that received dexmedetomidine spent more time within RASS goal and less time over sedated. The strategy of lorazepam dosing (i.e., continuous infusion titration without bolus dosing) may have contributed to over sedation, but was utilized in this manner to maintain blinding. There were no differences noted in ventilator-free days, ICU length of stay (LOS), or 28-day mortality between groups. Bradycardia, defined as a heart rate of less than 60 beats/min, occurred more often in the dexmedetomidine group but this did not lead to any differences in hemodynamic compromise. In the subset of patients with sepsis, dexmedetomidine was associated with a mean of ~3 more days alive without delirium or coma (p = 0.09), 6 more ventilator free days (p = 0.02), and a 25% absolute risk reduction in 28-day mortality (16% with dexmedetomidine vs. 41% with lorazepam, p = 0.03); no significant findings were identified in the non-septic subset [19]. The subsequent DESIRE trial set-out to further evaluate clinical outcomes amongst septic mechanically ventilated patients managed with dexmedetomidine

Table 1: Select Trials Evaluating Dexmedetomidine for Sedation in Mixed Medical-Surgical Populations

Investigator	Study Design/ Subjects	Treatment Groups	Primary Endpoint(s)	Other Results
Pandharipande PP, et al.(2007)[ſ] [12]	P, DB, R, MCT > 18 y/o ExpectedMV > 24 hours N = 103	• Dexmedetomidine (n = 52) 0.15 – 1.5 mcg/kg/hr • Lorazepam (n = 51) 1 – 10 mg/hr • Rescue medication: F, Pr • Titrated to RASS determined by medical team	Median days alive without delirium or coma: D7 vs. L 3*	• Time spent within 1 point of RASS goal via nurse assessment: D 80% vs.L 67%*and physician assessment: D 67% vs. L 55%* • Median days with over sedation: D 1 vs. L 2* • Bradycardia (HR < 60 bpm): D 17% vs. L 4%*
Riker RR, et al. (2009)[ſ] [13]	P, DB, R, MCT ≥ 18 y/o Expected MV > 72 hours N = 366	• Dexmedetomidine (n = 244) SD 0.8 mcg/kg/hr (optional 1 mcg/kg LD) (max 1.4 mcg/kg/hr) • Midazolam (n = 122) SD 0.06 mg/kg/hr (optional 0.05 mg/kg LD) (max 0.1 mg/kg/hr) • Titrated to RASS -2 to +1 • Rescue medication: F, M, H	Time within target RASS: D 77.3% vs. M 75.1%†	• Median time to extubation (days): D 3.7 vs. M 5.6* • Delirium prevalence: D 54% vs. M 76.6%* • Mean delirium-free days: D 2.5 vs. M 1.7* • Bradycardia (HR < 40 bpm): D 42.2% vs. M 18.9%*
Jakob SM, et al. (2012)[ſ] [18]	P, DB, R, MCT ≥ 18 y/o ExpectedMV > 24 hours N = 500	• Dexmedetomidine (n = 249) 0.2 – 1.4 mcg/kg/hr • Midazolam (n = 251) 0.03 – 0.2 mg/kg/hr • Titrated to RASS 0 to -3 • Rescue medication: F, Pr	Time at target sedation without rescue medication: D 60.7% vs. M 56.6%†	• Median RASS during study drug: D -0.9 vs. M -1.5* • Median duration of MV (hr): D 123 vs. M 164* • Median ICU LOS (hr): D 211 vs. M 243† • Bradycardia: D 14.2% vs. M 5.2%*
Jakob SM, et al. (2012)[ſ] [18]	P, DB, R, MCT ≥ 18 y/o ExpectedMV > 24 hours N = 498	• Dexmedetomidine (n = 251) 0.2 – 1.4 mcg/kg/hr • Propofol (n = 247) 0.3 – 4 mg/kg/hr • Titrated to RASS 0 to -3 • Rescue medication: F, M	Time at target sedation without rescue medication: D 64.6% vs. Pr 64.7%†	• Median RASS during study drug: D -1.0 vs. Pr -1.7* • Median duration of MV (hr): D 97 vs. Pr 118† • Median ICU LOS (hr): D 164 vs. Pr 185† • Bradycardia: D 13% vs. Pr 10.1%†

*p < 0.05; †p > 0.05, [ſ]industry sponsored
DB: Double-Blind; D: Dexmedetomidine; F: Fentanyl; H: Haloperidol; HR: Heart Rate; LD: Loading Dose; L: Lorazepam; LOS: Length of Stay; MV: Mechanical Ventilation; M: Midazolam; MCT: Multicenter Trial; Pr: Propofol; P: Prospective; R: Randomized; RASS: Richmond Agitation Sedation Scale; SD: Starting Dose

(n = 100) versus a non-dexmedetomidine based sedation regimen (n = 101; propofol, midazolam, and analgesia) [20]. Contrary to the MENDS trial, no significant differences in ventilator-free days or 28-day mortality were noted [20]. Differences in comparator groups and limited Power secondary to smaller than expected differences in 28-day mortality may have played a role in the findings.

The SEDCOM trial was a prospective, double-blind, multicenter study to compare time within target sedation goals (RASS of -2 to +1) in critically ill, mechanically ventilated patients randomized to dexmedetomidine or midazolam [13]. The majority of patients were admitted to the medical ICU (> 80%) for treatment of pneumonia and severe sepsis with mean APACHE II scores of ~18-19. There was no difference between groups in the primary outcome of percent of time patients spent within sedation target range; however, there was an approximately 2 day difference in time to extubation in favor of the dexmedetomidine group (median, 3.7 days vs. 5.6 days; p = 0.01). There was also lower delirium prevalence and more delirium-free days in the dexmedetomidine group, with a number needed to treat of five patients to avoid development of delirium. To note, the mean maintenance dose in the dexmedetomidine group was 0.83 mcg/kg/hr and 63% of patients received open-label bolus midazolam to achieve adequate sedation vs. 49% in the midazolam group (p= 0.02). Bradycardia, defined as a heart rate of less than 40 beats/min, occurred more often with dexmedetomidine but there was no difference in bradycardia requiring an intervention between groups [13]. The MIDEX trial, a subsequent prospective, multicenter, double-blind, non-inferiority, randomized controlled trial [14] that compared dexmedetomidine to midazolam in mechanically ventilated patients, consisted mainly of medical patients (> 60%) with median Sequential Organ Failure Assessment (SOFA) scores of 7. No difference was noted in the percent of time at target sedation (RASS 0 to -3) without rescue medication between the dexmedetomidine (median dose 0.45 mcg/kg/hr) and midazolam groups. However, similar to the SEDCOM trial, the median duration of mechanical ventilation was approximately 2 days shorter in the dexmedetomidine group (median, 123 hours vs. 164 hours; p = 0.03). Bradycardia and hypotension occurred more often in the dexmedetomidine group [14].

The PRODEX trial methodology was identical to that of MIDEX with the exceptions of the comparator group (propofol) and the rescue sedative agent (midazolam via intravenous bolus) [14]. There was no difference in the percent of time at target sedation without rescue medication between the dexmedetomidine (median dose 0.925 mcg/kg/hr) and propofol groups. Unlike the MIDEX trial, the duration of mechanical ventilation did not differ between the dexmedetomidine and propofol groups, likely attributable to propofol's short duration of action and rapid / predictable patient awakening upon discontinuation. There were also no differences in the incidences of bradycardia and hypotension between the groups.

The available literature indicates that dexmedetomidine is an appropriate sedative optionin the intubated mixed medical-surgical population and can be safely utilized for durations greater than 24 hours. In order to facilitate mechanical ventilation, infusion rates greater than the FDA approved maximum dose may be required, as demonstrated in the SEDCOM trial where 61% of patients required an average dose between 0.7 to 1.4 mcg/kg/hr [13]. Clinically, dexmedetomidine has been associated with a decreased prevalence and duration of delirium [12,13] and a shorter duration of mechanical ventilation [13,14] vs. benzodiazepines, but may not have an advantage over propofol. Such findings have also been observed via meta-analysis. [21]In regards to safety and tolerance, bradycardia appears to be the most common adverse drug event associated with dexmedetomidine, with occurrence rates of 13 to 40% depending on the definition utilized.[12-14] Collectively, dexmedetomidine is an effective and safe sedative option to facilitate light sedation in the medical-surgical population and may lead to improved clinical outcomes versus other sedation strategies, particularly benzodiazepines.

Post-operative cardiac surgery population

The focus of most trials evaluating dexmedetomidine in the post-operative cardiac surgery population has been on reducing post-operative delirium (POD). This is likely due to the high incidence of POD, reported in approximately 10-50% of post-cardiac surgery patients [22-25] and the positive data associating dexmedetomidine with delirium resolution and decreased delirium prevalence in the mixed medical-surgical population [13]. The requirement of sedation and analgesia post-operatively is also in many cases short-term due to fast-track to extubation pathways in cardiac surgery patients [26,27], limiting the need of primarily evaluating sedation assessment.

Shehabi and colleagues evaluated dexmedetomidine (n = 152) vs. morphine (n = 147) continuous infusions (with rescue propofol and morphine) in post-operative, mechanically ventilated, cardiac surgery patients in a randomized, double-blinded fashion [28]. The dexmedetomidine and morphine infusions were titrated to a Motor Activity Assessment Scale (MAAS) score of 2 to 4. There was no difference between study groups in the primary outcome of the percentage of patients who developed delirium via the CAM-ICU by post-operative day five; however, there were 3 less days spent with delirium in the dexmedetomidine vs. morphine group (2 days vs. 5 days, p = 0.031). The authors' evaluated the MAAS within target range as a secondary outcome and found no differences between groups (dexmedetomidine 0.1 – 0.7 mcg/kg/hr, 75.2% vs. morphine 10 – 70 mcg/kg/hr, 79.6%, p = 0.516). The majority of patients in both groups required propofol infusions in the first six hours (dexmedetomidine 78.3% vs. morphine 83%) although the requirement thereafter significantly decreased (dexmedetomidine 38.1% vs. morphine 34%). The use of dexmedetomidine was associated with more bradycardia, defined as a heart rate less than 55 beats/minute (16.5% vs. 6.1%, p = 0.006), but did not lead to interventions, comparable to trials in the medical/surgical ICU population. Although the use of open-label morphine in the dexmedetomidine group may have a confounding bias, the use was small and comparable between groups and increases external validity as patients in the post-operative setting will likely require analgesic medication.

Maldonado and colleagues [29] carried out an open-label, prospective, randomized clinical trial in post-operative cardiac surgery patients comparing dexmedetomidine (n = 30)

vs. propofol (n = 30) vs. midazolam (n = 30) with as needed fentanyl in all groups on the development of POD. The study drugs were titrated to a goal Ramsay Sedation Scale (RSS) of 3 during mechanical ventilation and delirium was assessed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria. The incidence of delirium was significantly higher in the propofol (50%) and midazolam (50%) groups by post-operative day three versus dexmedetomidine (3%) (p <0.001). The authors' did not report time spent within RSS goal or median score; therefore, it is difficult to interpret sedation efficacy and the open-label design may introduce potential bias. Recently, Djaiani and colleagues [30] prospectively evaluated dexmedetomidine (n = 91) vs. propofol (n=92) on the incidence of delirium in post-op cardiac surgery patients. Morphine and hydromorphone were administered as needed for analgesia while haloperidol was available for first-line delirium treatment. The Sedation Agitation Scale (SAS), which is a valid and reliable sedation assessment tool [4], was utilized to assess sedation quality with a goal of 4. Delirium, which was assessed via the CAM-ICU, occurred less often in the dexmedetomidine vs. propofol group by post-operative day five (17.5% vs. 31.5%, respectively, p = 0.028) and resolved 1 day earlier (median duration of delirium, 2 days vs. 3 days; p = 0.04). There were no differences in median SAS scores at 24 hours between groups (dexmedetomidine SAS 4 vs. propofol SAS 4, p = 0.13).

In the post-operative cardiac surgery population, dexmedetomidine may be an appropriate sedative option compared to standard therapy, such as propofol and midazolam, particularly in regards to minimizing POD. Dexmedetomidine also appears to be well-tolerated. Bradycardia did occur more often in the DEXCOM trial in the dexmedetomidine vs. morphine group (p = 0.006), but was not associated with increased interventions [28]. Lastly, in a meta-analysis [31] that included both prospective and retrospective trials to evaluate safety and efficacy of dexmedetomidine vs. other sedation strategies, dexmedetomidine was associated with a lower incidence of POD, shorter duration of mechanical ventilation, and increased bradycardia. Additional well-designed studies using validated sedation assessment tools are needed to further evaluate the sedation efficacy of dexmedetomidine in the post-cardiac surgery population. Lastly, practitioners should remain cognizant that despite dexmedetomidine's analgesic sparing effects [9] concurrent opioid therapy should be utilized to address pain in the post-operative setting.

Neurocritical care populations

In the neurocritical care population mild to moderate sedation levels are important to facilitate frequent neurological exams. A preferred sedative for this population would exhibit a rapid onset and short duration of action. Historically, propofol has been the sedative of choice, but dexmedetomidine may be an appropriate alternative. In a prospective, randomized, double-blinded, crossover study [32] dexmedetomidine displayed cognitive improving effects in awake, intubated patients with and without brain injury vs. propofol. However, there are no large prospective, randomized trials that evaluate sedation efficacy of dexmedetomidine vs. other sedation agents as a primary outcome in the neurocritical care population.

In a single-center, prospective, observational trial [33] in 198 traumatic brain injury (TBI) patients expected to require mechanical ventilation for at least 48 hours, the mean time at target RASS (0 to -2) was assessed between four different sedation strategies (dexmedetomidine only, propofol only, dexmedetomidine and propofol, or neither agent). Comparisons were made among patients-days with a particular sedation strategy as patients were not exclusively enrolled to one group due to the lack of randomization. There was a total of 1028 patient days; 222 days in the dexmedetomidine only group, 599 days in the propofol only group, 148 days in the dexmedetomidine and propofol group, and 59 days in the neither group. The dexmedetomidine only group spent more time within target RASS than propofol only (mean daily estimate: dexmedetomidine 15.9 hours vs. propofol 13.2 hours, p = 0.01) and the neither group (mean: 11.5 hours, p = 0.01). There were no differences found between fentanyl uses for analgesia in any sedation group. Hypotension, defined as a systolic blood pressure less than 90 mmHg, did occur more often in the dexmedetomidine only and dexmedetomidine and propofol group vs. propofol only group (p=0.01, respectively), but interventions were not reported. The observational nature of this trial and small treatment differences found within time spent at target RASS limit the clinical applicability, but the results are hypothesis generating and encouraging. Two recent meta-analyses [34,35] evaluated the use of dexmedetomidine for sedation in the neurocritical population and suggested sedation efficacy, but noted the lack of available literature.

Overall, there is a need for large, prospective, multicenter, randomized controlled trials in the neurocritical care population evaluating the efficacy and safety of dexmedetomidine vs. other sedation agents. In lieu of such data, the efficacy and safety of dexmedetomidine in this population remains unknown. Dexmedetomidine use is not recommended over current standards of care and should only be considered at the treating team's discretion with evaluation of risks and benefits of therapy.

NONINVASIVE VENTILATION

The use of dexmedetomidine to facilitate patient tolerance to NIV is an appealing option given its minimal respiratory depressive effects, particularly in comparison to alternative options such as benzodiazepines, propofol, and opioids. To date, only a handful of studies have been published evaluating the utility of dexmedetomidine in critically ill adult patients requiring NIV, predominantly small, single-center investigations.

In 2008, Akada and colleagues published the results of their single-center, non-comparative pilot trial evaluating dexmedetomidine in 10 critically ill patients intolerant to NIV (RSS of 1 and a RASS of +1 or greater) [15]. The majority of patients were receiving NIV secondary to post-operative respiratory failure (6/10) utilizing the continuous positive airway pressure mode (9/10); the severity of illness was not detailed. Dexmedetomidine 0.2 – 0.7 mcg/kg/hr was associated with achievement of target sedation levels (mean RSS 2.94, mean RASS -1.23) and successful weaning from NIV in all patients (i.e., no cases of intubation) with no episodes of bradycardia or hemodynamic instability. This was the first trial to demonstrate the feasibility of dexmedetomidine for facilitating NIV amongst

patients intolerant to such therapy; however, the lack of a comparator group hindered the ability to gain insight regarding this agent's place in practice.

Two subsequent larger single-center trials compared dexmedetomidine to midazolam infusions amongst patients intolerant to NIV (Table 2) [16,17]. The first of which was double-blinded, and included 40 patients (median APACHE II of 21.5) managed with bilevel positive airway pressure (BiPAP) for chronic obstructive pulmonary disease (COPD) exacerbation. The primary intent was to compare the sedative efficacy of the two agents. Compared to midazolam, dexmedetomidine was associated with lighter levels of sedation as evidenced by statistically significant lower mean RSS (~2 – 2.5 vs. ~3) and higher SAS (~4 vs. 3) at various time points. There were no cases of NIV failure in either group [16]. In 2012, Huang and colleagues published the largest trial to date (n=62) and the first to focus on clinically relevant outcomes. All patients had acute cardiogenic respiratory failure and intolerance of NIV; baseline median left ventricular ejection fraction was ~47%, PaO2/FiO2 ratio was ~180, arterial pH ~7.2, and APACHE II score ~22, with no differences in baseline characteristics between those randomized to dexmedetomidine versus midazolam. Using predetermined criteria, patients randomized to dexmedetomidine exhibited a statistically significant lower intubation rate (21% vs. 45%; number needed to treat of 4) as well as shorter median duration

Table 2: Select Trials Evaluating Dexmedetomidine for Noninvasive Ventilation

Investigator	Study Design/ Subjects	Treatment Groups	Primary Endpoint(s)	Other Results
Senoglu N, et al. (2010) [15]	P, DB, R, SCT > 18 y/o, COPD exacerbation requiring NIV (BiPAP), RSS 1 and SAS ≥ 1 N = 40	• Dexmedetomidine (n = 20) 1 mcg/kg LD over 10 min, then 0.5 mcg/kg/hr (max 0.7 mcg/kg/hr) • Midazolam (n = 20) 0.05 mg/kg LD over 10 min, then 0.1 mg/kg/hr (max 0.2 mg/kg/hr) • Titrated to RSS 2 to 3, SAS 3 to 4, and BIS > 85 • If inadequate sedation after 2 titrations, study stopped • No additional sedatives / analgesics allowed	RSS • Statistically lower in D vs. M group, 2 – 24 hrs after study drug initiation SAS • Statistically higher in D vs. M group, 8 – 24 hrs after study drug initiation BIS • Statistically higher in D vs. M group at all time points Oversedation • D (n=0) vs. M (n=1) Inadequate Sedation • D (n=0) vs. M (n=2)	NIV Failure • No cases in either study group Respiratory Parameters • No difference between D vs. M groups in pH, RR, Pa02, PaCO2 Hemodynamics • HR: statistically lower in D vs. M group, 1 – 24 hrs after initiation • BP: statistically lower in D vs. M group during initial 2 hrs only
Huang Z et al. (2012) [16]	P, OL, R, SCT > 18 y/o, acute cardiogenic respiratory failure requiring NIV, NIV failure due to patient refusal N = 62	• Dexmedetomidine (n = 33) 0.2 – 0.7 mcg/kg/hr (optional 1 mcg/kg LD) • Midazolam (n = 29) 0.05 – 0.1 mg/kg/hr (optional 0.05 mg/kg LD) • Titrated to RSS 2 to 3 • No mention of use of rescue sedatives / analgesics	Need for Intubation • D 21% vs. M 45%*	Median duration of NIV (hours)‡ • D 57.5 vs. M 93.4* Median ICU LOS (days) • D 4.9 vs. M 8.5* ICU Mortality • D 6.1% vs. M 10.3%† Adverse Events • Bradycardia: D 18% vs. M 0%* • Hypotension: D 12% vs. M 17%† • Delirium: D 3% vs. M 14%†
Devlin J, et al. (2014)∫ [17]	P, DB, R, PC, 2-center trial Adult, NIV ≤ 8 hrs, SBP >90 mmHg, HR > 50 bpm N = 33	• Dexmedetomidine (n = 16) 0.2 – 0.7 mcg/kg/hr • Placebo (n = 17) • Max study duration: 72 hrs • Titrated q30 min to SAS 3 - 4 • Rescue medications: F, M, H	NIV Tolerance • D: OR 1.44 (0.44 – 4.7) † • Median time spent NIV tolerant: D 99% vs. P 67%†	• % patients w/ a NIV intolerance episode: D 50% vs. P 47%† • NIV failure req.intubation D 31% vs. P 29%† • Median time to intubation D 22 hrs vs. P 37 hrs† • Mean HR: D 81 vs. P 98 bpm*

* $p < 0.05$; † $p > 0.05$; ‡ Outcome evaluated only in the subset of patients who did not require intubation (Dexmedetomidine, n=26; Midazolam, n=16), ∫ industry sponsored

BiPAP: Bilevel Positive Airway Pressure Ventilation; BIS: Bispectral Index; BP: Blood Pressure; COPD: Chronic Obstructive Pulmonary Disease; D: Dexmedetomidine; DB: Double-Blind; F: Fentanyl; H: Haloperidol; HR: Heart Rate; L: Lorazepam; LOS: Length of Stay; M: Midazolam; MCT: Multicenter Trial; MV: Mechanical Ventilation; NIV: Non-Invasive Ventilation; OL: Open-Label; P: Prospective;Pao2: Partial Pressure of Arterial Oxygen; Paco2: Partial Pressure of Arterial Carbon Dioxide; PC: Placebo Controlled; R: Randomized; RASS: Richmond Agitation Sedation Scale; RSS: Ramsay Sedation Score; RR: Respiratory Rate; SAS: Sedation-Agitation Scale; SCT: Single Center Trial.

of NIV (57.5 vs. 93.4 hours, amongst the subset of patient not requiring intubation). The median ICU length of stay was ~3.5 days shorter for the dexmedetomidine group. Bradycardia (defined as a HR less than 40 bpm) occurred in ~1 out of every 5 patients treated with dexmedetomidine, but no patients required intervention. Although the open-label design introduces potential bias, the results are promising and supportive of future well-designed trials to further evaluate the potential superiority of dexmedetomidine over midazolam infusions for facilitating NIV in intolerant patients [17].

Most recently, a double-blind placebo-controlled trial was conducted, enrolling 33 critically ill patients receiving NIV [18]. In contrast to the previous investigations, patients did not have to exhibit NIV intolerance in order to be enrolled; rather, it was hypothesized that early routine use of dexmedetomidine in patients receiving NIV would improve NIV tolerance and help avoid failure. Patients enrolled were hemodynamically stable, with a mean APACHE II of ~15-16, and predominantly suffered from pneumonia or COPD/asthma-related respiratory failure, with a mean time from NIV initiation to study drug initiation of less than 5 hours. Dexmedetomidine was not associated with a significantly greater odds of tolerating NIV compared to placebo (odds ratio [OR] 1.44; 95% confidence interval [CI] 0.44 – 4.7), which was also the case for the subset of patients intolerant to NIV at baseline (OR 2.71; 95% CI 0.49 – 15.07). Similarly, there was no difference in the incidence of NIV failure requiring intubation. Interestingly, the median time spent at the desired level of sedation was 100% in both study groups; rescue medication administration was numerically higher in the placebo group although not statistically significant. The small sample size, use of an invalidated NIV intolerance scoring system, and most importantly, inclusion of patients who were NIV tolerant at baseline (67% of enrolled patients) may have hindered the utility of dexmedetomidine in this trial.

Collectively, available data suggests that dexmedetomidine is a viable option to help facilitate NIV. Similar to other pharmacologic options, dexmedetomidine use should be reserved for patients exhibiting intolerance to NIV (i.e., data does not support pre-emptive use). In such patients, dexmedetomidine may improve clinical outcomes compared to benzodiazepines, but additional well-designed trials are needed to confirm preliminary findings.

CONCLUSION

Dexmedetomidine has received considerable attention over recent years, particularly via evaluation of its safety and efficacy in mechanically ventilated patients. The majority of available literature has focused on the medical-surgical ICU population, in which dexmedetomidine has demonstrated the ability to maintain mild to moderate levels of sedation comparable to current standards of care while reducing the duration of mechanical ventilation and delirium prevalence compared to benzodiazepine based sedation. Practitioners should remain cognizant that dexmedetomidine infusion rates of 0.7 to 1.5 mcg/kg/hr are often required to facilitative invasive mechanical ventilation. In the post-operative cardiac surgery population, available data indicates that dexmedetomidine may be an appropriate sedative alternative to reduce the incidence and duration of POD; in the neurocritical care population, its utility largely remains unknown. Preliminary data indicates dexmedetomidine 0.2 – 0.7 mcg/kg/hr can be utilized to facilitate NIV in patients intolerant to such therapy and may improve clinical outcomes in comparison to midazolam. Overall, the collective body of literature (invasive and NIV) indicates that use of dexmedetomidine for durations greater than 24 hours appears tolerable. Bradycardia occurs commonly with dexmedetomidine and should be considered prior to and during administration.

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