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# Evaluation of Sedation Outcomes Following Increased Dexmedetomidine Use in the ICU

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**Objective:** To evaluate sedation practices following a dexmedetomidine guideline update in the ICU.

**Design:** Single-center, retrospective chart review.

**Setting:** Tertiary academic medical center.

**Patients:** Patients were included in this analysis if they were admitted to the ICU and were ordered for continuous infusion sedatives or opioids from September to November 2016 (PRE) and from September to November 2017 (POST). Patients were excluded from this analysis if they met any of the following criteria: mechanical ventilation less than 12 hours, admitted with acute neurologic injury, burn of greater than 20% total body surface area, chronic tracheostomy, admitted to the neuroscience or cardiac surgery ICU, on extracorporeal membrane oxygenation support, or received an infusion of neuromuscular blockers.

**Interventions:** Patients admitted during a restricted dexmedetomidine prescribing guideline were compared with patients admitted during an expanded prescribing guideline.

**Measurements and Main Results:** Of the 1,426 patients evaluated for inclusion, 427 patients met the criteria in this analysis. Of these, 217 patients were in the PRE and 210 patients in the POST. A majority of patients were excluded for admission to neuroscience or cardiac surgery ICU. Dexmedetomidine was used in 13.8% of encounters in the PRE and 51.9% of encounters in the POST ( $p < 0.001$ ). The median duration of mechanical ventilation was 49 hours (24–110 hr) in the PRE and 47.5 hours (26–98 hr) in the POST ( $p = 0.8$ ). ICU length of stay was a median of 136 and 121 hours in the PRE and POST, respectively ( $p = 0.2$ ). The median hospital length of stay was 296 and 326 hours in the PRE and POST, respectively ( $p = 0.35$ ).

After controlling for possible confounders, ventilation time remained unchanged between the PRE and POST ( $p = 0.98$ ).

**Conclusions:** The expansion of a hospital dexmedetomidine prescribing guideline resulted in an increased use of dexmedetomidine but was not associated with a difference in length of mechanical ventilation.

**Key Words:** benzodiazepines; critical care; delirium; dexmedetomidine; mechanical ventilation; sedation

Sedative and analgesic medications are often used in the ICU for the management of pain, agitation, delirium, and assistance with ventilator synchrony (1). The 2018 Society of Critical Care Medicine guidelines for the management of pain, agitation/sedation, delirium, immobility, and sleep disruption conditionally recommend the use of propofol or dexmedetomidine as a first-line sedative over the use of benzodiazepines (2). The guidelines do not make a recommendation supporting either propofol or dexmedetomidine when compared with each other (2).

Propofol and benzodiazepines both agonize  $\gamma$ -aminobutyric acid and suppress respiratory drive facilitating ventilator synchrony (1). Dexmedetomidine, a potent agonist of the  $\alpha_2$  receptor, does not significantly suppress respiratory drive and can be useful in achieving a light level of sedation (3). When compared with benzodiazepines, dexmedetomidine has been associated with decreased duration of mechanical ventilation but has shown an inconsistent impact on the prevalence of delirium (4–7). Significant differences in clinical endpoints, such as duration of mechanical ventilation or delirium, have not been seen when comparing dexmedetomidine and propofol (6).

Initially due to higher cost and alternative sedation strategies, dexmedetomidine had been restricted at our institution. In June 2017, institutional dexmedetomidine prescribing guidelines were expanded to allow for its use as a first-line sedative in mechanically ventilated patients. The purpose of this analysis was to evaluate patient outcomes before and after institutional dexmedetomidine guideline changes.

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## MATERIALS AND METHODS

A single-center, retrospective chart review analysis was performed at Brigham and Women's Hospital, a 793-bed, acute, tertiary care, academic medical center in Boston, MA. Partners Healthcare institutional review board (IRB) approval was obtained before the start of this study (IRB protocol number: 2018P001856). A hospital reporting system was used to identify all adult patients who were admitted to the ICU and received continuous infusion sedatives or opioids between September 1, 2016, to November 30, 2016 (PRE), and September 1, 2017, to November 30, 2017 (POST). Patients were included in the analysis if they were mechanically ventilated via endotracheal tube and received a continuous infusion of sedatives and/or opioids for greater than 12 hours. Patients were excluded from this analysis if they met any of the following criteria: admitted with acute neurologic injury, burn of greater than 20% total body surface area, chronic tracheostomy, admitted to the neuroscience or cardiac surgery ICU, on extracorporeal membrane oxygenation support, or received an infusion of neuromuscular blockers.

Before the expansion of prescribing guidelines at Brigham and Women's Hospital, dexmedetomidine could be used in patients who were unable to be extubated despite optimization of sedatives and analgesics, or if there were contraindications to usual sedative or adjunctive medications. Following guideline expansion, as long as pain needs were adequately assessed and treated, dexmedetomidine could be prescribed in mechanically ventilated patients without restriction.

Data collected included patient demographics, pertinent medical history and baseline laboratory values, Acute Physiology and Chronic Health Evaluation (APACHE) II score at the time of ICU admission, duration of mechanical ventilation, ICU length of stay, and hospital length of stay. Sedation, delirium, and pain assessments were collected hourly using the Richmond Agitation and Sedation Scale (RASS) score, Confusion Assessment Method for the ICU (CAM-ICU) score, and Critical-Care Pain Observation Tool (CPOT) scores, respectively. Data collected also included total sedative, opioid, and antipsychotic requirements. Infusion rates of analgesics and sedatives, sedation and pain assessments, and antipsychotic requirements were collected up until extubation or tracheostomy. Chart review of daily respiratory therapist progress notes was used to calculate percentage of days receiving a spontaneous breathing trial.

The primary endpoint of this analysis was duration of mechanical ventilation, defined as the number of hours between intubation and extubation or tracheostomy to a maximum of 14 days. Secondary endpoints included ICU and hospital length of stay, depth of sedation (light sedation defined as RASS  $-2$  to  $+1$  and deep sedation defined as  $-5$  to  $-3$ ), prevalence of delirium (defined as CAM-ICU-positive delirium days), prevalence of pain (defined as CPOT score of  $> 2$ ), and percentage of days receiving a spontaneous breathing trial.

Continuous data were analyzed using paired *t* test (parametric data, expressed as mean [SD]) or Mann-Whitney *U* test (non-parametric data, expressed as median [interquartile range]) when appropriate. Chi-square test was used when appropriate for categorical data. A sample size of 145 patients in each arm was calculated assuming an average duration of mechanical ventilation

of 118 hours with a 20% relative risk reduction based on an 80% power and an  $\alpha$  of 0.05 (6).

Post hoc subgroup analyses were conducted to assess usage and sedation outcomes when comparing PRE and POST medical and surgical patients. Included in these analyses was a comparison of all patients who received dexmedetomidine versus all patients who did not regardless of PRE versus POST status.

Post hoc multivariate regression models were constructed to compare ventilation time before and after guideline change after controlling for sex, ethnicity, weight, APACHE II score, type of ICU, percentage of days receiving a spontaneous breathing trial, median RASS, exposure to benzodiazepines, dexmedetomidine, and antipsychotics.

## RESULTS

A total of 1,420 patients were evaluated for inclusion, of which 427 patients met inclusion criteria. The majority of patients were excluded due to admission to the neuroscience or cardiac surgery ICU. Patient baseline characteristics are presented in **Table 1**. Of the 427 patients included, 217 patients were in the PRE and 210 patients in the POST. Dexmedetomidine use increased from 13.8% of encounters in the PRE to 51.9% in the POST ( $p < 0.001$ ), whereas midazolam decreased from 27.5% of encounters to 13.8% ( $p = 0.003$ ). There was no significant difference in propofol and opioid usage in the PRE and the POST (**Fig. 1**). The median duration of mechanical ventilation was 49 hours (24–110 hr) in the PRE and 47.5 hours (26–98 hr) in the POST ( $p = 0.8$ ). The percentage of days containing a spontaneous breathing trial did not change between the PRE (60.2%) and the POST (60.7%). There was no difference seen in ICU length of stay or hospital length of stay between groups (**Table 2**).

Median RASS scores were  $-3$  ( $-1$  to  $-4$ ) in both the PRE and POST ( $p < 0.001$ ) (**Fig. 2**). There was no significant difference found in the percent of patients with light sedation in the PRE (45.5%) versus the POST (47.1%); however, we did see a trend toward lighter sedation in the POST ( $p = 0.08$ ). Total daily doses and median duration of all sedatives and opioids did not differ between the PRE and the POST (Table 2).

There was no significant difference found in CAM-positive delirium days ( $p = 0.77$ ) or the use of antipsychotics ( $p = 0.57$ ) between the PRE and the POST. Days unable to assess decreased from 37.9% in the PRE to 28.8% in the POST ( $p < 0.001$ ). The prevalence of positive CPOT scores decreased from 20.4% in the PRE to 17.2% in the POST ( $p < 0.001$ ).

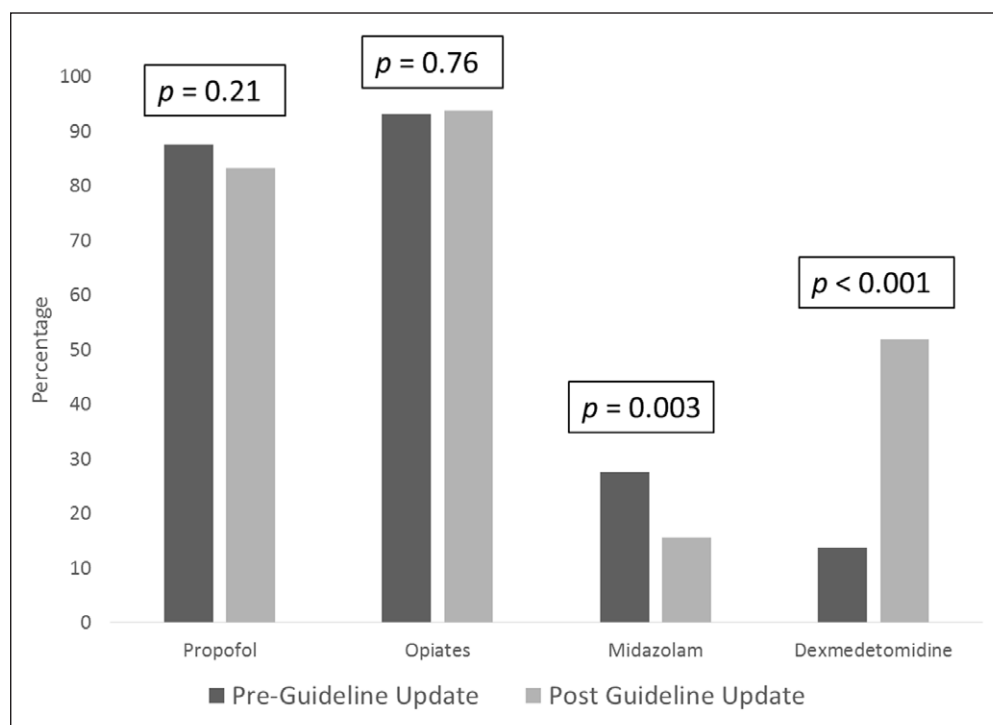
In the post hoc subgroup analysis for patients admitted to the medical ICU, there was no significant difference in the median length of mechanical ventilation, ICU stay, or hospital stay. Medical patients in the PRE group were more deeply sedated than the POST ( $p < 0.001$ ). There was a significant decrease in positive CPOT scores but no difference in positive CAM-ICU days in the POST ( $p = 0.82$ ) (**Table 3**).

For patients admitted to the surgical ICU, there was no significant difference in the median length of mechanical ventilation or hospital length of stay. ICU length of stay was significantly shorter in the POST group ( $p = 0.03$ ). Surgical patients in the PRE group were more deeply sedated than in the POST ( $p < 0.001$ ). There

**TABLE 1. Baseline Characteristics of the Study Groups**

Variable	Pre-Guideline Group, n = 217	Post-Guideline Group, n = 210	p
Male, n (%)	135 (62)	114 (54)	0.09
Age (yr), median (IQR)	66 (54–75)	62 (51–72)	0.09
Ethnicity, n (%)			0.30
Caucasian	166 (77)	156 (74)	
African American	22 (10)	14 (6)	
Hispanic	14 (6)	19 (9)	
Asian	3 (1)	8 (4)	
Other	1 (0.5)	3 (1)	
Unknown/withheld	11 (5)	10 (5)	
Weight (kg), median (IQR)	78.7 (66.5–93.5)	76.9 (64.5–92.9)	0.55
Unit, n (%)			0.82
Medical	116 (53)	109 (52)	
Surgical	101 (47)	101 (48)	
Acute Physiology and Chronic Health Evaluation II, median (IQR)	25 (19–30)	23 (18–30)	0.51

IQR = interquartile range.



**Figure 1.** Sedative and opioid use. Percentage of sedative and opioid use between the PRE and POST groups.

was a significant decrease in positive CPOT scores ( $p < 0.001$ ), but there was no difference in positive CAM-ICU days in the POST ( $p = 0.23$ ) (Table 3). Antipsychotic usage did not change between the PRE and POST surgical groups, but the POST had a significantly ( $p = 0.004$ ) decreased total daily dose of fentanyl equivalents.

Among all patients evaluated, patients who received dexmedetomidine had a significantly longer duration of mechanical ventilation

compared with those who did not (65 vs 42 hr;  $p = 0.004$ ). ICU length of stay (150 vs 118 hr;  $p < 0.001$ ) and hospital length of stay (398 vs 280 hr;  $p < 0.001$ ) were also significantly longer in patients who received dexmedetomidine. Patients receiving dexmedetomidine had significantly lighter RASS scores ( $-2$  [ $-1$  to  $-3$ ] vs  $-3$  [ $-1$  to  $-4$ ];  $p < 0.001$ ) with an increase in positive CPOT scores (16.2% vs 22.8%;  $p < 0.001$ ); however, there was a significant increase in positive CAM-ICU days (64.8% vs 73.6%) and a decrease in negative CAM-ICU days (35.2% and 26.4%;  $p = 0.003$ ).

After controlling for possible confounders with post hoc multivariate regression models, ventilation time remained unchanged between the PRE and the POST (odds ratio,  $-0.22$ ;  $p = 0.98$ ).

## DISCUSSION

This before-after analysis was conducted to evaluate the effect of liberalizing a dexmedetomidine prescribing guideline on sedative administration and clinical outcomes, such as duration of mechanical ventilation, level of sedation, delirium, and pain. We observed a greater percentage of patients in the POST group received dexmedetomidine, while the use of midazolam decreased. Use of propofol and opioids did not change between groups. In our

**TABLE 2. Sedation Outcomes and Opioids/Sedatives of the Study Groups**

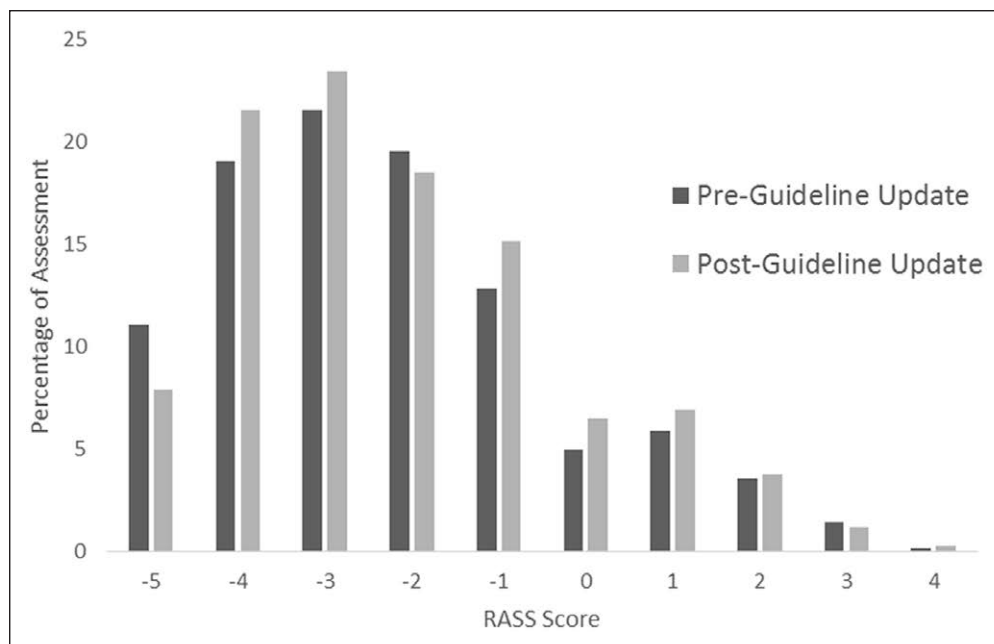
Variable	Pre-Guideline Group, n = 217	Post-Guideline Group, n = 210	p
Length of mechanical ventilation (hr), median (IQR)	49 (24–110)	47.5 (26–98)	0.80
Length of ICU stay (hr), median (IQR)	136 (87–245)	121 (79–207)	0.20
Length of hospital stay (hr), median (IQR)	296 (191–507)	326 (207–543)	0.35
Richmond Agitation and Sedation Scale score, median (IQR)	–3 (–1 to –4)	–3 (–1 to –4)	< 0.001
CAM-ICU (d), n (%)	n = 446	n = 547	0.77
Positive	308 (69.1)	373 (68.2)	
Negative	138 (30.9)	174 (31.8)	
CAM-ICU (d), n (%)	272 (37.9)	221 (28.8)	< 0.001
Unable to assess			
Critical-Care Pain Observation Tool, n (%)	n = 5,889	n = 5,861	< 0.001
Positive > 2	1,203 (20.4)	1,006 (17.2)	
Negative ≤ 2	4,686 (79.6)	4,855 (82.8)	
Propofol (mg), median (IQR)	2,159 (941–4,055)	2,307 (1,142–4,194)	0.059
Propofol (hr), median (IQR)	31 (15–67)	30 (15–58)	0.653
Dexmedetomidine (µg), median (IQR)	493 (245–852)	558 (257–1,134)	0.17
Dexmedetomidine (hr), median (IQR)	21 (9–32)	22 (11–44)	0.401
Midazolam (mg), median (IQR)	21.8 (8.3–51.5)	23.8 (10.6–51.1)	0.39
Midazolam (hr), median (IQR)	13 (8–36)	15 (8–29)	0.582
Hydromorphone (mg), median (IQR)	21.7 (9.3–42.8)	14.1 (7.4–28.1)	0.045
Hydromorphone (hr), median (IQR)	44 (11–102)	57 (29–128)	0.258
Fentanyl (µg), median (IQR)	772 (416–1,529)	836 (414–1,557)	0.63
Fentanyl (hr), median (IQR)	39 (19–77)	34 (16–62)	0.114
Fentanyl equivalents (µg), median (IQR)	846 (433–1,652)	874.5 (450–1,681)	0.55
Opioids (hr), median (IQR)	38 (19–80)	36 (17–68)	0.499

CAM-ICU = Confusion Assessment Method for the ICU, IQR = interquartile range. Fentanyl equivalents defined as 100 µg fentanyl:1.5 mg hydromorphone (17).

analysis, despite the increase in dexmedetomidine and decrease in midazolam use, there was no difference in duration of mechanical ventilation. Previous studies have shown that the use of dexmedetomidine is associated with a decrease in length of mechanical ventilation when compared with benzodiazepines (4–6). Jakob et al (6) showed that there was no difference in length of mechanical ventilation between dexmedetomidine and propofol. Our findings could be due to several factors. First, we use propofol in the majority of patients who require continuous sedation. It is unclear if this is simply due to familiarity or because patients required medications for respiratory depression to assist with ventilator synchrony. Second, when we use benzodiazepines, we use significantly lower doses on average than studies comparing this drug class to dexmedetomidine (5, 8, 9). It is well established that administration of high doses of benzodiazepines for prolonged periods of time, especially in critically ill patients with organ dysfunction, contributes to an increase in duration of mechanical ventilation. There

was also no difference in length of ICU or hospital stay between our PRE and POST group. This is in line with previous studies comparing dexmedetomidine to alternative sedatives (4–6, 10).

There was a significant difference in RASS scores in our study despite identical median and interquartile ranges. We believe this to be based on the distribution reflecting a decreased prevalence of RASS –5 and an increase in RASS –1, 0, and +1. When categorizing RASS scores into deep and light sedation, there was a trend toward lighter sedation in our POST group. Light sedation (Ramsay 1–2) has shown to reduce duration of mechanical ventilation and ICU length of stay when compared with deep sedation (Ramsay 3–4) (11). Although our level of sedation was statistically different, our patient populations were relatively similarly sedated overall. This is most likely due to our predominant use of propofol as a sedative of choice in both populations. Although there was no difference in number of positive CAM-ICU days between the PRE and POST, we did see an increase in our subgroup of all patients



**Figure 2.** Richmond Agitation and Sedation Scale (RASS) score PRE versus POST comparison. Comparison of level of sedation between the PRE and POST groups.

standard of care and associated this with the increased number of assessments. These results are in contrast to previous trials, which have not shown a difference of delirium when using dexmedetomidine over benzodiazepines (4, 6, 12).

In our POST group, we saw a decrease in positive CPOT scores. Studies have shown that dexmedetomidine may have opioid-sparing effects, especially in the perioperative setting (13, 14). Although our analysis showed no difference in total daily opioid use between the PRE and POST groups, the decline in positive CPOT scores could be attributed to lighter sedated patients' ability to request medications to better control their pain. A decline in positive CPOT scores is important not only to ensure patient comfort but also

**TABLE 3. Post Hoc Subgroup Analysis: Medical Versus Surgical Patients**

Variable	Pre-Guideline Group, n = 116	Post-Guideline Group, n = 109	p	Pre-Guideline Group, n = 101	Post-Guideline Group, n = 101	P
	Medical			Surgical		
Length of mechanical ventilation (hr), median (IQR)	70 (28–129)	61 (36–118)	0.48	41 (21–93)	38 (17–68)	0.26
Length of ICU stay (hr), median (IQR)	120 (84–238)	140 (85–240)	0.78	139 (88–261)	100 (71–187)	0.03
Length of hospital stay (hr), median (IQR)	281 (161–480)	318 (198–499)	0.18	344 (223–530)	328 (220–595)	0.98
Richmond Agitation and Sedation Scale score, median (IQR)	-3 (-2 to -4)	-3 (-1 to -4)	< 0.001	-2 (-1 to -3)	-2 (0 to -3)	< 0.001
CAM-ICU (d), n (%)	n = 263	n = 346	0.82	n = 183	n = 201	0.23
Positive	204 (69.1)	271 (68.2)		104 (56.8)	102 (50.7)	
Negative	59 (30.9)	75 (31.8)		79 (43.2)	99 (49.3)	
CAM-ICU (d), n (%)	194 (42.5)	134 (27.9)	< 0.001	78 (29.9)	87 (30.2)	0.93
Unable to assess						
Critical-Care Pain Observation Tool, n (%)	n = 3,670	n = 3,768	0.02	n = 2,219	n = 2,093	< 0.001
Positive > 2	604 (16.5)	545 (14.5)		599 (27.0)	461 (22.0)	
Negative ≤ 2	3,066 (83.5)	3,223 (85.5)		1,620 (73.0)	1,632 (78.0)	

CAM-ICU = Confusion Assessment Method for the ICU, IQR = interquartile range.

who received dexmedetomidine versus all patients who did not. Separately, we found a significant decrease in unable to assess in our PRE versus POST group, PRE versus POST medical subgroup, and all dexmedetomidine versus no dexmedetomidine subgroup. This is most likely due to lighter sedation providing the opportunity for assessment of delirium. Ruokonen et al (7) found a similar increase in delirium with dexmedetomidine in comparison with

because targeted pain control through analgo-sedation has shown improved outcomes in the duration of mechanical ventilation (15).

Multivariate regression models were constructed in order to control for potential confounders in our primary outcome of length of mechanical ventilation. We chose to control for benzodiazepine use because previous studies have shown that exposure to benzodiazepines is associated with prolonged ventilation time



(4–6). RASS scores were included as lighter sedation has shown to reduce the length of mechanical ventilation (10). Spontaneous breathing trials were included because these have been associated with decreased length of mechanical ventilation (16). Despite controlling for these confounders, we found no difference in length of mechanical ventilation between the PRE and POST groups. With a decreased use of midazolam and a trend toward lighter sedation, one would anticipate a significant difference in our primary outcome. Riker et al (5) found that with mean doses of approximately 5 mg/hr of midazolam (extrapolated from 0.056 mg/kg dosing and median weight of patients) and median duration of more than 5 days, duration of mechanical ventilation was significantly increased when compared with dexmedetomidine. As benzodiazepine doses in our practice are magnitudes lower than in previous studies, we believe that the decreased midazolam use had less of an impact on mechanical ventilation. An additional cause for no significant difference in mechanical ventilation could be the overall high usage of propofol and low usage of midazolam in both PRE and POST regardless of the significant decrease in use. Shehabi et al (12) found similar results with no significant difference in median number of ventilator-free days despite a difference in midazolam use of 11.9% in usual care and 2.9% in dexmedetomidine.

There are several limitations to this study. This was a single-center, retrospective analysis which can limit generalizability. With chart review analysis, we are limited by incomplete and inconsistent documentation. Because spontaneous breathing trial data were collected through respiratory therapist notes, incorrect documentation could have impacted these values. There is also the possibility that our hospital reporting system did not capture all patients for assessment.

## CONCLUSIONS

This analysis found that after an expansion of dexmedetomidine prescribing guidelines, our institution saw a decreased use of midazolam with an increased use of dexmedetomidine. Despite this difference, we found no difference in the duration of mechanical ventilation, but did observe an increase in delirium in overall patients who received dexmedetomidine. This could be due to lighter sedation providing more opportunities for assessments and positive CAM-ICU days.

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The authors have disclosed that they do not have any potential conflicts of interest.

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