

# Comparison of dexmedetomidine and propofol in mechanically ventilated patients with sepsis: A pilot study

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## ABSTRACT

**Objective:** To compare the effects of a propofol-based versus dexmedetomidine-based sedation regimen for mechanically ventilated patients with sepsis.

**Methods:** Single-center, randomized, open-label interventional study of critically ill patients admitted to the intensive care unit with sepsis and respiratory failure requiring mechanical ventilation. Patients were sedated with either propofol or dexmedetomidine.

**Results:** Thirty-six patients with sepsis and respiratory failure requiring mechanical ventilation were randomly assigned to receive sedation with either dexmedetomidine or propofol. Fentanyl was used for analgesia in both groups. The primary end point was duration of mechanical ventilation, and secondary end points included 28-day mortality, the duration of ICU stay, and the duration of vasopressor support. There was a non-statistically significant trend toward decreased duration of mechanical ventilation in the dexmedetomidine group ( $p = 0.107$ ), and multivariable analysis demonstrated a small to moderate effect size in the sample. There were no significant differences in 28-day mortality, duration of ICU stay, or duration of vasopressor requirement. No patients required discontinuation of study drug due to adverse effects.

**Conclusions:** Although underpowered for statistical significance, there was a trend toward decreased duration of mechanical ventilation with dexmedetomidine. More studies with higher patient enrollment are needed to determine whether the duration of mechanical ventilation in patients with sepsis who receive sedation with dexmedetomidine is reduced when compared to propofol.

**Keywords:** sepsis, respiratory failure, ventilators, mechanical, propofol, dexmedetomidine, sedation

## INTRODUCTION

Patients requiring mechanical ventilation often need sedation to maintain comfort. Historically, benzodiazepines and propofol were the preferred sedatives in the intensive care unit (ICU), but dexmedetomidine has recently had increased usage.<sup>1-3</sup> Benzodiazepines and propofol primarily act at the

GABA<sub>A</sub> receptor; dexmedetomidine is an imidazole compound that is a specific  $\alpha_2$ -adrenoceptor agonist. Although the mechanism of action of dexmedetomidine is not completely understood, the primary mechanism likely involves presynaptic activation of the  $\alpha_2$ -adrenoceptor and subsequent inhibition of the release of norepinephrine and termination of pain signal propagation. Additionally, post-synaptic activation of  $\alpha_2$ -adrenoceptors in the central nervous system inhibits sympathetic activity, resulting in decreased blood pressures and heart rates.<sup>4</sup> This combination of effects results in analgesia, sedation, and anxiolysis, and patients sedated with dexmedetomidine

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are more arousable and have minimal respiratory depression.<sup>5</sup>

Since its initial approval by the FDA in 1999 for sedation of intubated and mechanically ventilated patients in the ICU, dexmedetomidine has been extensively studied in well-designed, randomized trials in comparison to other sedative drugs. In 2007, the MENDS trial compared dexmedetomidine to lorazepam and found that dexmedetomidine was associated with less delirium and more time spent at the targeted level of sedation.<sup>6</sup> The SEDCOM trial in 2009 compared dexmedetomidine to midazolam and demonstrated a reduced duration of mechanical ventilation and less delirium in patients sedated with dexmedetomidine.<sup>7</sup> The PRODEX and MIDEX trials were conducted jointly and compared dexmedetomidine to propofol and midazolam, respectively. These trials showed a significantly decreased duration of mechanical ventilation with dexmedetomidine compared to midazolam, and a non-significant decrease in the duration of mechanical ventilation with dexmedetomidine compared to propofol.<sup>8</sup> When the sepsis subgroup in the MENDS trial was reanalyzed, a significant mortality benefit was found for patients sedated with dexmedetomidine.<sup>9</sup>

Most sedatives, including propofol and benzodiazepines, suppress the innate immune response.<sup>10</sup> In contrast, dexmedetomidine stimulates the innate immune response in animal studies.<sup>11,12</sup> Immune potentiation with dexmedetomidine has been considered a possible contributing factor to the mortality benefit observed in septic patients sedated with dexmedetomidine rather than lorazepam, which is associated with immune suppression. In current practice, non-benzodiazepine sedation (with propofol or dexmedetomidine) is recommended due to the association of benzodiazepines with adverse clinical outcomes, including longer duration of mechanical ventilation, increased ICU length of stay, and the development of delirium.<sup>3,13,14</sup> The PRODEX trial included a broad spectrum of patients requiring mechanical ventilation and did not find a statistically significant difference in duration of mechanical ventilation between dexmedetomidine and propofol. Thus, it is unknown whether patients with sepsis requiring mechanical ventilation

will benefit from sedation with dexmedetomidine, and most centers do not consider one sedative superior to the other for patients in this group.

Since current data suggest a possible benefit with dexmedetomidine for sedation of mechanically ventilated patients with sepsis and current guidelines recommend sedation with either dexmedetomidine or propofol for mechanically ventilated patients, we designed the PRO-DEFENSE (Propofol versus Dexmedetomidine for Mechanically Ventilated Patients with Sepsis) to test the hypothesis that dexmedetomidine, when compared with propofol, reduces the duration of mechanical ventilation.

## **MATERIALS AND METHODS**

This prospective, open-label, randomized trial was conducted in the ICUs at University Medical Center in Lubbock, TX, between September 2014 and February 2016. The protocol was approved by the Institutional Review Board of the study center, and all patients or legally authorized representatives provided written informed consent. The study was designed by the investigators. Data were collected by the investigators and analyzed by the Clinical Research Institute at Texas Tech University Health Sciences Center in Lubbock, TX.

Eligible patients were age 18 to 89 years old, had a diagnosis of sepsis, and required mechanical ventilation. Sepsis was defined as a potential source of infection with  $\geq 2$  of the following criteria: 1) temperature  $< 36.0^{\circ}\text{C}$  or  $> 38.0^{\circ}\text{C}$ ; 2) heart rate  $> 90/\text{minute}$ ; 3) respiratory rate  $> 20/\text{minute}$  or  $\text{PaCO}_2 < 32 \text{ mmHg}$ ; 4) WBC count  $< 4000/\mu\text{L}$ ,  $> 12000/\mu\text{L}$ , or  $> 10\%$  bands. Exclusion criteria included the following patients: 1) documented allergies to propofol, dexmedetomidine, fentanyl, eggs or egg products, or soy or soy products; 2) heart rates less than 50/minute or grade 2 or 3 AV heart block; 3) mean arterial pressures less than 55mmHg despite fluid resuscitation and vasopressor support; 4) triglyceride levels  $> 400 \text{ mg/dL}$ .

Patients who met criteria were randomized into either a dexmedetomidine treatment group or a propofol treatment group on a 1:1 basis using a random

number generator and sealed envelopes. Due to the different appearances of propofol (an emulsion) and dexmedetomidine, the study was not blinded. Detailed information regarding sedative and analgesic therapy prior to initiation of study drug, baseline demographics, and severity of illness were obtained at the time of enrollment after consent was signed.

After randomization, sedatives used before study enrollment were titrated off, and titration of the study drug was initiated. Fentanyl was used for analgesia for both study groups. Propofol was initiated at 5 mcg/kg/minute and titrated every 5 minutes by 5 mcg/kg/minute. The maximum dose of propofol was 80 mcg/kg/minute. Dexmedetomidine was initiated at 0.2 mcg/kg/hour and titrated every 5 minutes by 0.1 mcg/kg/hour to a maximum dose of 1.4 mcg/kg/hour. The Richmond Agitated and Sedation Scale (RASS) target was  $-1$  to  $+1$ . Patients with inadequate sedation scores on their assigned drug received supplemental sedation with midazolam or lorazepam as needed based on nursing and physician assessment.

The primary end point was duration of mechanical ventilation. Secondary end points included the duration of ICU stay, the duration of vasopressor support, a composite outcome (number of days of ventilator support plus number of ICU days plus number of days of vasopressor support), the percent alive at discharge, transfer, or at 28 days of hospitalization, the number of patients who needed a second sedative in addition to their study drug, and the number of patients who required discontinuation of their sedation medication due to unacceptable side effects.

The median duration of ventilator support and interquartile range for each study group were calculated, and the two study groups were compared using non-parametric testing with the Mann-Whitney U test. Similar calculations were made for the length of ICU stay, duration of vasopressor support, and the composite score. The number of survivors in the two groups was tabulated and reported in terms of frequency and relative percentages. A chi-square test was used to compare the two study groups. Similar calculations were made for the number of patients needing supplemental sedation and for the number of patients requiring their study drug to be discontinued. P values  $\leq 0.05$

were considered statistically significant. Assuming an equal sample size allocation with 5% ( $\alpha = 0.05$ ) level of significance and 80% power, a total sample size of 260 (130 per study group) was needed to calculate a 35% reduction in duration of mechanical ventilation. Assuming a 20% attrition rate due to mortality, the figure was adjusted to 163 individuals in each study group (total of 326 patients). This analysis was based on non-parametric testing with the Mann-Whitney-Wilcoxon test. An interim analysis was planned after the first 100 patients had been enrolled in the study.

## RESULTS

From September 9, 2014, through March 1, 2016, 42 patients with respiratory failure requiring mechanical ventilation and sepsis were enrolled in the PRO-DEFENSE study. Six patients were subsequently excluded, and 36 were included in the analysis: 19 in the propofol group and 17 in the dexmedetomidine group. Due to the slow enrollment, an interim analysis was conducted in March 2016, and the study investigators decided to discontinue the trial.

The characteristics of the patients at inclusion in the study were similar in the two groups (Table 1). The sources for infection included the respiratory tract ( $n = 31$ ), urinary tract ( $n = 7$ ), abdomen ( $n = 3$ ), cellulitis ( $n = 2$ ), and miscellaneous ( $n = 4$ ) (several patients had more than one source). The  $\text{PaO}_2:\text{FiO}_2$  ratio was  $205 \pm 166$  in the propofol group and  $200 \pm 62$  in the dexmedetomidine group. Because the attrition rate was higher than expected, a preliminary analysis was conducted using the non-parametric Mann-Whitney U test to compare continuous covariates and Fisher's Exact test to compare categorical covariates. Baseline covariates were compared to identify any clinical differences between groups (Table 2). The time from intubation to randomization (3.0; interquartile range [IQR]: 6.4 hours for the dexmedetomidine group vs. 10.0; IQR: 18.3 for the propofol group,  $p = 0.010$ ) and the use of vasopressors (82.4% for dexmedetomidine group vs. 47.4% for propofol group,  $p = 0.041$ ) were the only statistically significant differences between the two groups.

In univariate analysis, the primary outcome (number of ventilator days) was shorter in the

**Table 1: Baseline characteristics of patients**

Parametric covariates	Dexmedetomidine (n = 17)		Propofol (n = 19)		p-value
	Mean	SD	Mean	SD	
Age	62.5	9.6	59.0	15.4	0.419
BMI	29.7	8.2	30.1	6.5	0.824
PEEP at 24 hrs.	6.0	1.8	7.2	3.0	0.253
PaO <sub>2</sub> :FiO <sub>2</sub> ratio at 24 hrs.	195	76	210	85	0.626
Ordinal covariates	Median	(Q1, Q3)	Median	(Q1, Q3)	p-value
SOFA score	11	(7, 14)	10	(8, 13)	0.924
APACHE2 score	19	(13, 20)	16.0	(12, 19)	0.349
Categorical covariates	Count	%	Count	%	p-value
Male	13	76%	9	47%	0.097
White	15	88%	19	100%	0.216
Hispanic	5	29%	7	37%	0.732
Transfer patients	7	41%	11	58%	0.505

dexmedetomidine group, but this did not reach statistical significance ( $p = 0.107$ ) (Table 3). The number of ICU days and the number of vasopressor days were similar in the two groups ( $p > 0.25$ ). The twenty-eight day mortality was 42.1% (8/19) in the propofol group and 52.9% (9/17) in the dexmedetomidine group ( $p = 0.249$ ). Given the possible difference in ventilator days, an adjusted analysis was used to address potential differences between groups at baseline. This multivariable analysis adjusted for potential differences in

age, BMI, and SOFA, and/or APACHE2 scores in the two study groups. All three competing models (SOFA, APACHE2, and SOFA and APACHE2) had similar p-values ( $p = 0.126$ ,  $p = 0.129$ ,  $p = 0.131$ ), and no covariates were significant factors ( $p > 0.10$ ). Based on this analysis, the estimated least-square mean difference between dexmedetomidine and propofol was 3.13 ventilator days (95% CI: -7.23 to 0.96 days,  $p = 0.129$ ). While this result did not reach significance ( $\alpha > 0.05$ ), the partial eta-squared of 0.073 (95%

**Table 2: Details of study drugs administered**

Non-parametric covariates	Dexmedetomidine (n = 17)		Propofol (n = 19)		p-value
	Median	(Q1, Q3)	Median	(Q1, Q3)	
Duration of study drug infusion (days)	2.8*	(1.5, 4.0)	3.0†	(1.3, 4.0)	0.603
Intubation to randomization (hrs)	3.0	(1.8, 8.25)	10.0	(4.2, 22.5)	0.010
Total fentanyl received ( $\mu\text{g}$ )	290	(100, 475)	478.8	(184, 1165)	0.096
Categorical covariates	Count	%	Count	%	p-value
Vasopressors used	14	82%	9	47%	0.041
Supplemental sedation	0	0.0%	0	0.0%	1.000
Adverse events from study drug	0	0.0%	0	0.0%	1.000

\* 2 missing values

† 4 missing values

**Table 3: Study outcomes**

Continuous outcomes	Dexmedetomidine (n = 17)		Propofol (n = 19)		p-value
	Median	IQR (Q3-Q1)	Median	IQR (Q3-Q1)	
Days of mechanical ventilation	3	(2.75, 5.75)	5	(3, 13)	0.107
Days of ICU stay	5	(3, 8)	6	(4, 14)	0.260
Days of vasopressor infusion*	2	(0, 3)	0	(0, 3.3)	0.376
Composite outcome* (sum the above)	10.5	(5.0, 18.25)	11.8	(9.8, 28.0)	0.202
Categorical outcomes	Count	%	Count	%	p-value
Mortality (28 days)	9	53%	8	42%	0.739

\*one outcome was missing value from each of the two groups.

CI: 0-0.259) corresponds to a small to moderate effect size in this sample. A power analysis suggested that 64 subjects in each group would be sufficient to probe an alpha of 0.05 at 80% power.

## DISCUSSION

In this single center, randomized trial comparing dexmedetomidine and propofol for sedation in mechanically ventilated patients with sepsis, there was no statistically significant difference in the duration of mechanical ventilation between patients who received dexmedetomidine and those who received propofol. There was a non-statistically significant trend toward decreased duration of mechanical ventilation in the dexmedetomidine group, and this trend remained after multivariate analysis. Secondary outcomes, including mortality, ICU days, and vasopressor days, were not different between the two groups. In the 36 patients who underwent randomization, no patients required discontinuation of the assigned sedative medication secondary to adverse effects.

This study was designed to determine whether the subset of mechanically ventilated patients with sepsis would have a difference in mechanical ventilation with dexmedetomidine compared with propofol. Although underpowered, the available data from our study suggest that mechanically ventilated patients with sepsis may have a decreased duration of mechanical ventilation when sedated with dexmedetomidine. Despite an increased severity of illness in the

dexmedetomidine group, this trend toward decreased duration of mechanical ventilation with dexmedetomidine remained after adjusted analysis.

Klompas, et al. recently evaluated dexmedetomidine, propofol, and benzodiazepines as sedatives in mechanically ventilated patients in a meta-analysis and noted a decreased time to extubation with dexmedetomidine compared to propofol and benzodiazepines and a trend toward a decreased incidence of ventilator-associated events with dexmedetomidine compared to propofol and benzodiazepines.<sup>15</sup> One limitation in this meta-analysis was the reduced use of dexmedetomidine compared to other sedative medications. However, this study provides additional evidence in support of an association between decreased duration of mechanical ventilation and sedation with dexmedetomidine. This analysis by Klompas did not demonstrate any differences in mortality.

Our trial has several limitations. First, enrollment was limited, which resulted in the study being underpowered to detect statistically significant differences. Differences in comorbidity in the two groups could also have influenced outcomes. There were differences between the two groups in the baseline requirement for vasopressors. However, this was factored in to the adjusted analysis. Second, this was a single center study, and therefore our results may not be generalizable to other institutions. Third, due to the technical difficulties with concealing propofol and dexmedetomidine infusions, our study was not blinded. Despite these limitations, this trial does reveal some clinically

important findings. First, both dexmedetomidine and propofol appear safe for use as sedatives in mechanically ventilated patients with sepsis. In this trial, no adverse effects requiring study drug discontinuation occurred. Second, despite being underpowered, there was a trend toward decreased duration of mechanical ventilation with dexmedetomidine, and this trend persisted after multivariable analysis. When interpreted in reference to recent meta-analysis by Klompas, this result emphasizes the potential importance of more studies comparing dexmedetomidine and propofol, particularly in patients with sepsis.

## CONCLUSIONS

Both dexmedetomidine and propofol appear to be safe sedatives in mechanically ventilated patients with sepsis. This study suggests a possible decrease in duration of mechanical ventilation in patients sedated with dexmedetomidine, but additional studies are needed to determine whether this is statistically significant.

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