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COMPARISON OF DEXMEDETOMIDINE AND PROPOFOL AS SEDATIVE IN MECHANICALLY VENTILATED PATIENTS WITH SEPSIS

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KEYWORDS :

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.1-3 Benzodiazepines and propofol primarily act at the

GABAA receptor; dexmedetomidine is an imidazole compound that is a specific α2-adrenoceptor agonist. Although the mechanism of action of dexmedetomidine is not completely understood, the primary mechanism likely involves presynaptic activation of the α2-adrenoceptor and subsequent inhibition of the release of norepinephrine and termination of pain signal propagation. Additionally, post-synaptic activation of α2-adrenoceptors in the central nervous system inhibits sympathetic activity, resulting in decreased blood pressures and heart rates.4 This combination of effects results in analgesia, sedation, and anxiolysis, and patients sedated with dexmedetomidineare more arousable and have minimal respiratory depression.5

Most sedatives, including propofol and benzodiazepines, suppress the innate immune response. In contrast, dexmedetomidine stimulates the innate immune response in animal studies.11,12 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. The protocol was approved by the Institutional Review Board of the study center, and all patients provided written informed consent. 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 ≥2 of the following criteria: 1) temperature <36.0°C or >38.0°C; 2) heart rate >90/minute; 3) respiratory rate >20/minute or PaCO2<32 mmHg; 4) WBC count <4000/μL, >12000/μL, 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 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 randomnumber 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.

Results

42 patients with respiratory failure requiring mechanical ventilation and sepsis were enrolled in the study. Six patients were subsequently excluded, and 36 were included in the analysis: 19 in the propofol group and 17 in the dexmedetomidine group.

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 PaO2:FiO2 ratio was 205 ± 166 in the propofol group and 200 ± 62 in the dexmedetomidine group. 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.

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	15.4	0.419
BMI	29.7	8.2	30.1	6.5	0.824
PEEP at 24 hrs.	6	1.8	7.2	3	0.253
PaO2:FiO2 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	(12, 19)	0.349

The primary outcome (number of ventilator days) was shorter in the dexmedetomidine group, but this did not reach statistical significance (p = 0.107) (Table 2). 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 inage, 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% CI: 0-0.259) corresponds to a small to moderate effect size in this sample.

Table 2: 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)	0.26
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

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.15 One limitation in this meta-analysis was the reduced use of dexmedetomidine 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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