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COMPARISON OF DEXMEDETOMIDINE VERSUS PROPOFOL FOR SEDATION IN MECHANICALLY VENTILATED PATIENTS AFTER CARDIOVASCULAR SURGERY

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Abstract

Many cardiovascular surgeries are fast-tracked to extubation and require short-term sedation. Dexmedetomidine and propofol have very different mechanisms of action and pharmacokinetic profiles that make them attractive sedative agents in this patient population. Recently, there has been increased use of dexmedetomidine in the intensive care unit (ICU), but few studies exist or have been published directly comparing both agents in this setting. We conducted a retrospective cohort study with patients admitted to the ICU after cardiovascular surgery from January through June 2011. Adult patients who underwent coronary artery bypass and/or cardiac valve surgery received either dexmedetomidine or propofol continuous infusion for short-term sedation after cardiovascular surgery. The primary end point was time (hours) on mechanical ventilation after surgery. Secondary end points included ICU length of stay (LOS), hospital LOS, incidence of delirium, and requirement of a second sedative agent. A total of 352 patients met study inclusion criteria, with 33 enrolled in the dexmedetomidine group and 319 in the propofol group. Time on mechanical ventilation was shorter in the dexmedetomidine group (7.4 hours vs. 12.9 hours, P = .042). No difference was seen in ICU or hospital LOS. The need for a second sedative agent to achieve optimal sedation (24% vs. 27%, P = .737) and incidence of delirium (9% vs. 7.5%, P = .747) were similar between both groups. Sedation with dexmedetomidine resulted in a significant reduction in time on mechanical ventilation. However, no difference was seen in ICU or hospital LOS, incidence of delirium, or mortality.

Introduction

The goal of sedation in mechanically ventilated patients is to keep them calm and without agitation to maximize patient comfort and ventilator synchrony.[1,2] There are several different classes of sedative medications available, each with distinct pharmacokinetic and pharmacodynamic properties, and different side-effect profiles that may limit their use. Clinicians must not only take into account efficacy but also side effects such as hemodynamic instability, delirium, and cost when selecting appropriate sedation for their patients.

Patients undergoing coronary artery bypass graft (CABG) surgery and/or aortic/mitral valve surgery are often fast-tracked to extubation within 1 to 6 hours and require short-term sedation and analgesia.[3,4] In addition to careful drug selection by the ICU team, nursing-driven sedation protocols, pharmacist intervention, and scheduled daily interruption of sedation have been shown to improve patient outcomes and decrease overall time on sedation.[5-7] Dexmedetomidine (Precedex™) and propofol (Diprivan™) have very different mechanisms of action and pharmacokinetic profiles that make them attractive sedative agents in this patient population.

Dexmedetomidine is a centrally acting, alpha-2 adrenergic receptor agonist approved in 1999 by the U.S. Food and Drug Administration (FDA) for sedation in mechanically ventilated patients during the first 24 hours and in nonintubated patients prior to and/or during surgical or nonsurgical procedures.[8] It is the first and only alpha-2 agonist approved by the FDA for sedation. Dexmedetomine has shown to be effective for sedation while reducing the incidence of delirium and need for opioids, as dexmedetomidine also has analgesic properties.[9-18] The most common side effects associated with the use of dexmedetomidine include hypotension (24%-54%) and bradycardia (5%-14%), which are concerning in this patient population and may limit dexmedetomidine's usage. Although dexmedetomidine is still a branded medication and has a significant acquisition cost, a recent cost-effectiveness analysis showed that continuous sedation with dexmedetomidine resulted in significantly lower total ICU cost compared to sedation with midazolam.[19] Results from the study showed that sedation with dexmedetomidine resulted in ICU savings of $9,679 on average compared with midazolam, primarily due to decreased ICU LOS costs and reduced mechanical ventilation costs.

Propofol is a sedative-hypnotic agent used in the induction or maintenance of anesthesia or sedation.[20] It has long been the standard medication for sedation due to its rapid onset, short duration of action, and relatively low cost, but it has an adverse effect profile that may be concerning in cardiovascular patients.[1,2] Severe hemodynamic instability, such as bradycardia

and hypotension, both of which commonly occur at standard doses, has been shown to be a use-limiting side effect.[21-24] Propofol is also formulated in a fat-based emulsion that can cause hypertriglyceridemia after prolonged use.[1,2,25,26] Although propofol has ideal pharmacokinetic properties for patients requiring short-term sedation, it does possess side effects that make it an unwarranted choice in some patients.

Sedation at Houston Methodist Hospital is managed by a nursing-driven protocol in which Richmond Agitation Sedation Scale (RASS) goals are selected by the intensivists, and nursing staff may titrate the sedation per protocol to achieve or maintain the selected RASS goal. All patients receiving sedation in the cardiovascular surgery ICU use the sedation protocol. Patients are scheduled for daily interruptions of sedation at 6:00 AM unless otherwise directed by the ICU staff. Both dexmedetomidine and propofol are available as formulary agents for sedation in patients with an expected sedation requirement of less than 24 hours. Recently, there has been an increased use of dexmedetomidine at our institution. This study was conducted to evaluate the efficacy and safety of dexmedetomidine and propofol for sedation after cardiovascular surgery.

Methods

Patients and Study Design

This study was a retrospective observational trial approved by the Houston Methodist Institutional Review Board. Houston Methodist Hospital (HMH) is a 900+ bed tertiary academic hospital located in the heart of the Texas Medical Center. The cardiovascular surgery ICU (CVICU) is a 40-bed unit that serves a diverse group of patients including cardiovascular surgery, ventricular assist devices, and heart and lung transplants.

The University Healthsystem Consortium (UHC) database was queried to identify all patients at HMH who had undergone a CABG and/or aortic/mitral valve surgery from January 1 to July 31 of 2011 (Figure 1). All identified patients were screened for inclusion or exclusion criteria. The inclusion criteria included adult patients (18+) located in the CVICU who required mechanical ventilation upon arrival to the ICU and received either dexmedetomidine or propofol as initial choice of sedative agent after surgery. Patients were excluded if they received both dexmedetomidine and propofol concomitantly for primary sedation or an alternative agent as primary sedation, had a prior solid organ transplant, or were pregnant or lactating. There was no randomization of patients into each cohort. The study was retrospective, and sedation orders for either dexmedetomidine or propofol were based on individual physician ordering. Patients receiving both dexmedetomidine and propofol concurrently after the operating room were excluded because an appropriate comparison of one agent versus the other could not be made in these patients. Baseline characteristics such as age, sex, ethnicity, type of cardiovascular surgery, and UHC admission severity of illness score were collected. The UHC admission severity of illness score is a scoring tool used by the UHC to classify patient illness based on comorbidities, baseline characteristics, and admission diagnosis.[27] The UHC Clinical Database/Resource Manager includes patient admission severity of illness and risk of mortality scores (mild, moderate, major, and extreme) generated from 3M™ All Patient Refined Diagnosis Related Groups software (3M Health Information Systems, Salt Lake City, UT), which accounts for 29 comorbidities that are correlated with resource utilization and severity of illness.

Sedation was managed by a nursing-driven protocol, which has been established since 2007. Data was collected retrospectively using electronic medical records and respiratory therapist ventilator records. The UHC database was used for patient disposition after hospital stay and billing charges.

The primary end point was time on mechanical ventilation, which was defined as the number of hours postoperatively that the patient required ventilator support after arrival to the CVICU. Secondary end points included ICU LOS (days), hospital LOS (days), use of a second sedative agent to achieve optimal sedation, time at which a second sedative agent was required to achieve optimal sedation (hours), monitoring of RASS and Confusion Assessment Method-ICU (CAM-ICU), incidence of delirium (defined as CAM-ICU+ documentation), hospital mortality, and discharge status.

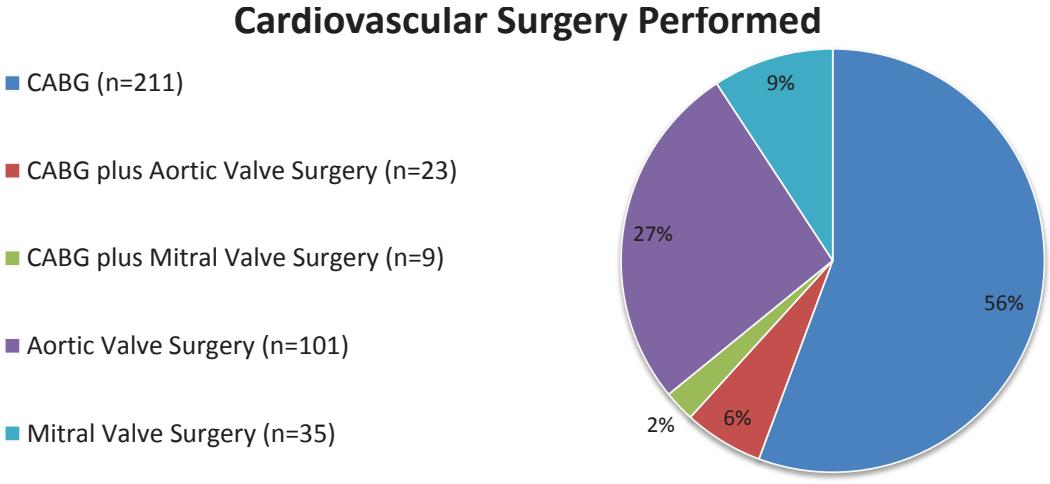

Figure 1. Type of cardiovascular surgery performed.

Statistical Analysis

Results were reported as mean +/- standard deviation or as a number value with a percentage. Continuous data variables were compared using the Student t-test. Categorical data was compared with the Chi-square test and Fisher exact test where appropriate. All *P*-values were 2-sided and data was statistically significant with an alpha of less than .05. All data was analyzed using Minitab® 16 (Minitab, Inc., State College, PA) statistical software. The pharmacoeconomic analysis was performed using TreeAge Software® (TreeAge Software, Inc., Williamstown, MA).

Results

Baseline Characteristics

A total of 401 patients were initially identified by the UHC database for study inclusion, with 49 of them excluded due to alternative choice of primary sedative agent, extubation upon arrival to the ICU, off sedation upon arrival to the ICU, or previous solid organ transplant. The other 352 patients ultimately met inclusion criteria during the enrollment period and were included in the final study analysis (Figure 2). Of these, 33 patients received initial sedation with dexmedetomidine and 319 patients received propofol. Baseline characteristics of the study population are summarized in Table 1. Patients were similar between the two groups except for age and the number of study subjects with a minor severity of illness upon admission. Patients in the dexmedetomine group were younger on average, 63 years old compared to 68 years old in the propofol group (*P* =.0106). Patients in the dexmedetomidine group also had a higher rate of minor admission severity of illness (33.3% vs. 18.5%, *P* = .042), but no difference was seen in patients with moderate, severe, or extreme severity of illness upon admission. No difference was seen between the two groups for type of cardiovascular surgery performed. More than 50% of patients had undergone coronary artery bypass surgeries (53%), while the remaining patients underwent either mitral or aortic valve surgeries or a combination of the three.

Primary and Secondary End Points

Patients receiving dexmedetomidine as primary sedation had a statistically significant reduction in time on mechanical ventilation compared to those who received propofol as the primary sedative agent (7.4 +/- 4.3 hours vs. 12.9 +/- 15.4 hours, *P* = .042) (Table 2). No difference was seen in ICU LOS. Hospital LOS was shorter in patients in the dexmedetomidine group (9.8 +/- 6.8 days vs. 12.4 +/- 7.4 days, *P* = .052), although a statistically significant reduction was not seen. No patients expired in the dexmedetomine group compared to two patients in the propofol group (0.06%, *P* > .99). There was no difference seen in discharge status between either

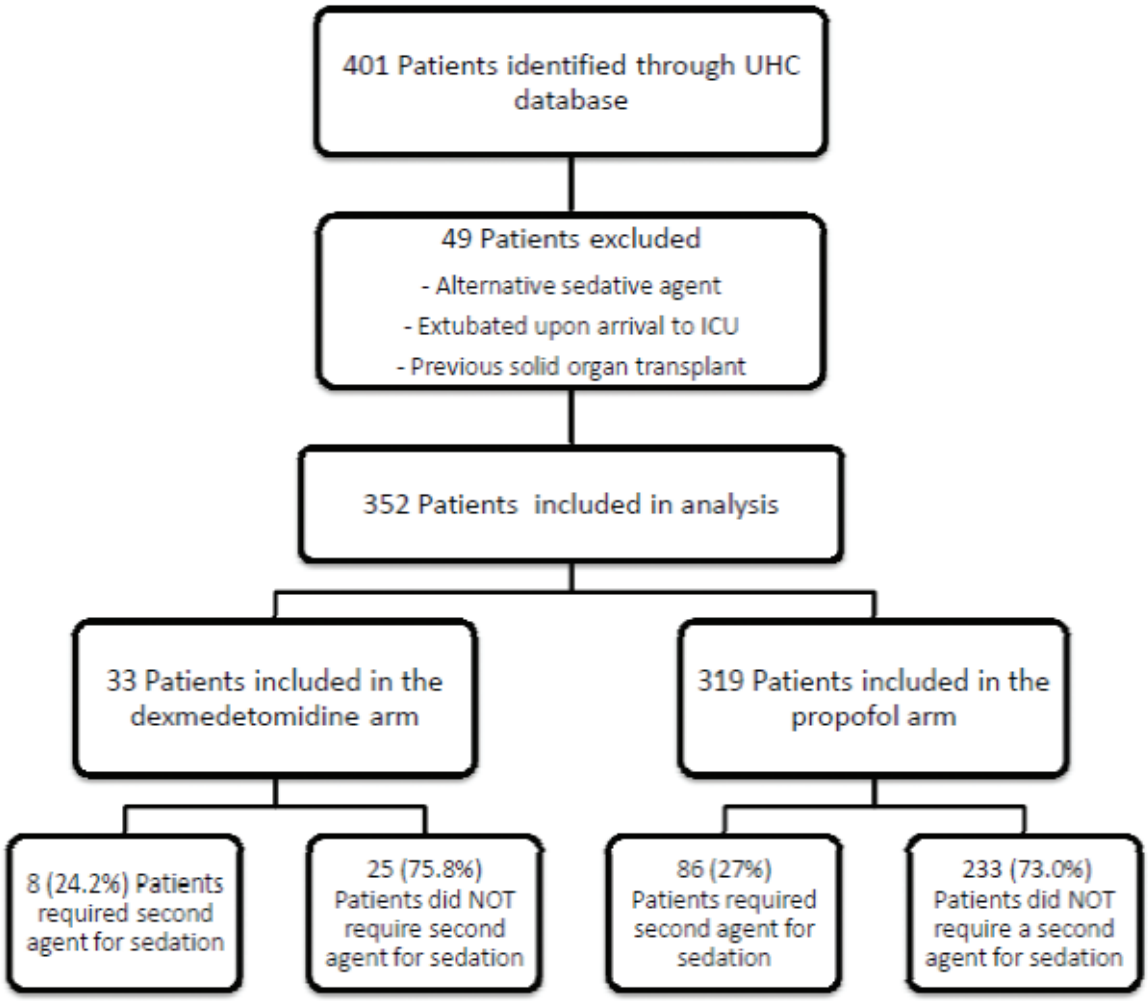

Figure 2. Patient enrollment

Variable	Dexmedetomidine (n = 33)	Propofol (n = 319)	*P* value
Mean +/- SD			
Age (years)	63 +/- 14.1	68 +/- 11.2	.0106
Weight (kg)	81.38 +/- 12.04	84.23 +/- 19.35	.4053
Height (cm)	174.15 +/- 4.30	171.96 +/- 10.30	.2274
No. patients (%)			
Gender			
Male	25 (75.8)	225 (70.5)	.5290
Ethnicity			
White	25 (75.8)	225 (70.5)	.5288
Black	1 (3.0)	22 (6.9)	.7098
Hispanic	2 (6.1)	26 (8.2)	1.000
Asian	3 (9.1)	8 (2.5)	.0737
Native American or Eskimo	0 (0)	1 (0.3)	.1790
Other	2 (6.1)	37 (11.6)	.5579
Admission Status			
Elective	21 (63.6)	173 (54.2)	.3011
Urgent	8 (24.2)	106 (33.2)	.2940
Emergent	4 (12.2)	11 (12.6)	.9450
Admission severity of illness			
Minor	11 (33.3)	59 (18.5)	.0420
Moderate	10 (30.3)	125 (39.2)	.3180
Major	10 (30.3)	124 (38.9)	.3350
Extreme	2 (6.1)	11 (3.4)	.4490
History of ethanol abuse			
Yes	4 (12.1)	4 (1.3)	.0035

Table 1. Baseline characteristics of study population.

treatment group, with 84.8% in the dexmedetomidine group and 72.7% in the propofol group (*P* = NS) being discharged to home or self-care.

A similar number of patients required an additional sedative agent to achieve optimal sedation (24% vs. 27%, *P* = .737). Propofol was supplementary added in all patients who were originally initiated on dexmedetomidine for sedation, while dexmedetomidine was most frequently used as adjunct sedation in patients originally initiated on propofol. Four patients on propofol received lorazepam as adjunct sedation. Time before requirement of a second sedative agent to achieve optimal sedation was similar for both groups (7.9 hours vs. 9.1 hours, *P* = .603).

RASS scores were documented in 100% of all study participants. CAM-ICU scores were documented in 79% of patients in the dexmedetomidine group compared to 84% in the propofol group (*P* = .411). Incidence of delirium (any vs. none) was similar between both groups (9.09% vs. 7.52%, *P* = .747).

A subgroup analysis was performed evaluating patients who only required one agent for sedation compared to patients requiring combination sedation with both dexmedetomidine and propofol (Table 3). Patients who required combination sedation had a longer duration of mechanical ventilation (10.3 hours vs. 18.1 hours, *P* < .001) and longer ICU and hospital LOS. A significant increase in delirium was also seen in patients on combination sedation (5% vs. 15%, *P* = .002).

Discussion

There are several different pharmacologic agents indicated for sedation in postoperative intubated patients. The updated recommendations from the Society of Critical Care Medicine and the American Society of Health-System Pharmacist Pain, Sedation and Analgesia guidelines, released in 2012, recommend first-line sedation with dexmedetomidine or propofol for most patients. Although these two agents will now be recommended as first-line agents over benzodiazepines, very few studies have directly compared them for sedation efficacy and patient outcomes. This study used a very large sample size of cardiac surgery patients compared to previous studies, although the number of patients who received propofol was much higher than those who received dexmedetomidine.[10,11,16,17] Houston Methodist Hospital is a large cardiovascular surgery center with many outside referrals, and the patients enrolled in this study were critically ill as evidenced in the admission severity-of-illness scores. While sedation with either dexmedetomine or propofol resulted in a relatively short time to

Variable	Dexmedetomidine (n = 33)	Propofol (n = 319)	*P* value
Mean +/- SD			
Hospital length of stay (days)	9.79 +/- 6.77	12.42 +/- 7.44	.052
ICU length of stay (days)	2.55 +/- 2.95	3.99 +/- 4.78	.091
Duration of mechanical ventilation (hours)	7.37 +/- 4.30	12.88 +/- 15.42	.042
No. patients (%)			
Hospital mortality (expired)	0 (0)	2 (0.6)	1.000
Incidence delirium (CAM-ICU+)	3 (12.0)	24 (9.0)	.747
Mean +/- SD			
Dexmedetomidine dosing (mcg/kg/hr)			
Average dose	0.489 +/- 0.13		
Maximum dose	0.602 +/- 0.15		
Propofol dosing (mcg/kg/min)			
dose, mean		29.50 +/- 10.63	
dose, maximum		36.38 +/- 13.49	
No. patients (%)			
Requirement of second sedative agent	8 (24.2)	86 (27.0)	.737
Dexmedetomidine	n/a	82 (95.3)	n/a
Propofol	8 (100)	n/a	n/a
Lorazepam	0 (0)	4 (4.7)	n/a
Mean +/- SD			
Time second agent started (hours)	7.90 +/- 12.99	9.13 +/- 10.92	.603

Table 2. Summary of study results.

extubation in our study, dexmedetomidine-based sedation resulted in a statistically significant reduction in time on mechanical ventilation compared to propofol. Decreasing the time on mechanical ventilation reduces the risk of ventilator complications such as pneumonia and stress ulcers, decreases the patient's risk of becoming delirious, and has significant cost implications. Although patients had shorter times on mechanical ventilation in the dexmedetomidine group, no difference was seen between the two groups in any of the other secondary end points, including LOS markers, incidence of delirium, or mortality. Although no statistically significant difference was seen in ICU LOS, the results trended toward a shorter ICU LOS, and this should be a primary end point evaluated in future studies comparing these two sedative regimens. More than 29% of patients required combination sedation with both dexmedetomidine and propofol or an additional agent. A subgroup analysis of patients in this study who received combination sedation with both agents had a statistically longer time on mechanical ventilation and longer ICU and hospital LOS. Patients who required more than one agent for sedation, even if being used exclusively during or around the time of extubation, may be at risk for increased time on mechanical ventilation and worse overall outcomes. Use of combination sedation and resulting outcomes needs to be addressed in future studies.

The presence of delirium in the ICU has been shown to increase time on mechanical ventilation, ICU and hospital LOS, and overall hospitalization cost.[28-31] Recent literature has focused on making healthcare providers more aware of delirium and how to properly screen and identify patients with delirium.[32] While assessment and documentation of delirium has improved, opportunities for improvement still exist, as described by Swan and colleagues.[33] In our study, 82% of patients were screened for delirium with the CAM-ICU assessment tool at least once during their ICU stay. Although the incidence of delirium was similar between both treatment groups, there was a significant increase in the number of CAM-ICU positive patients in those who received combination sedation with dexmedetomidine and propofol compared to patients who received just one agent. This data demonstrates that patients who require additional sedation may be at an increased risk for the development of delirium and subsequent adverse outcomes.

This study is not without limitations. First, the study design was retrospective in nature using an electronic medical record, the UHC database for outcomes and billing data, and respiratory care ventilator data. With retrospective data collection, identifying whether a side effect was caused by a medication or the

Variable	Single-agent sedation with either dexmedetomidine or propofol (n = 258)	Combination sedation with propofol and dexmedetomidine (n = 94)	*P* value
Mean +/- SD			
Duration of mechanical ventilation (hours)	10.27 +/- 10.79	18.12 +/- 21.48	.000
Hospital length of stay (days)	11.6 +/- 6.34	13.8 +/- 9.61	.013
ICU length of stay (days)	3.4 +/- 3.35	5.2 +/- 6.94	.001
No. patients (%)			
Hospital mortality (expired)	0 (0)	2 (2.1)	.071
Incidence delirium (CAM-ICU+)	13 (5)	14 (14.9)	.002

Table 3. Comparison of single versus combination sedation.

relative hemodynamic instability that is seen in postoperative cardiovascular surgery patients is difficult to determine. For this reason, side effect data was not reported. Data comparing side effects has been captured in previous studies, but this study design did not allow the researchers to establish an appropriate causal relationship.[10,11]

Another limitation was the large disparity between the number of patients who received dexmedetomidine compared to propofol as their primary sedative agent. Being retrospective in nature, there was no randomization of patients to either medication, and medication orders were based on individual physician prescribing. Physician selection of medication could have been a source of bias in this study. The data from this study demonstrates that although there has been a trend towards increased use of dexmedetomidine, it mostly is used as a second agent to optimize sedation. The significant difference in sample size may have lead to some unbalance in baseline characteristics between the groups. The mean age and percentage of patients with minor severity-of-illness scores were different between the two groups, which may have lead to a difference in the primary outcome. Another limitation is that data was not collected regarding additional medications that were prescribed during sedation, such as antipsychotics or opioids, which may have altered a patient's level of sedation and affected their time on mechanical ventilation and other outcomes.

Careful selection of sedative agents combined with a proven systematic method of handling sedation, such as a validated sedation protocol, has improved our ability to decrease time on mechanical ventilation and improve overall patient outcomes.[5-7] The addition of a daily interruption of sedation protocol, intervention by a clinical pharmacist who provides recommendations for the best choice of sedative agent and monitors side effects and efficacy, and continued analysis of sedation protocols are all important methods for improving sedation in the ICU. A cause and effect relationship cannot be proven with retrospective studies. Future prospective, randomized studies should continue to evaluate the efficacy, safety, and cost implications of short-term sedation with agents such as dexmedetomidine, propofol, and benzodiazepines.

Conclusion

This study evaluated dexmedetomidine versus propofol for sedation in patients after cardiovascular surgery. Sedation with dexmedetomidine resulted in a significant reduction in time on mechanical ventilation. No difference was seen in ICU or hospital LOS, incidence of delirium, or mortality. In patients requiring both agents for sedation, there was an increase in time on mechanical ventilation, ICU and hospital LOS, and the incidence of delirium.

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