



Dexmedetomidine versus midazolam and propofol for sedation in critically ill patients: Mining the Medical Information Mart for Intensive Care data

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Background: The benefits of dexmedetomidine on reducing mortality and length of intensive care unit (ICU) stay are still controversial. We aimed to evaluate the superiority of dexmedetomidine by comparing it with midazolam and propofol.

Methods: Subjects who were given dexmedetomidine, midazolam and propofol exclusively as sedatives in the Beth Israel Deaconess Medical Center between 2001 and 2012 were identified from the Medical Information Mart for Intensive Care (MIMIC) III database. Univariate, multivariate and stratified analysis was performed to compare the mortality and length of ICU stay between the dexmedetomidine, midazolam and propofol groups. To compare the depth of sedation between the midazolam and propofol group, we used propensity score matching (PSM) to create comparable units and their Richmond Agitation Sedation Score (RASS) were analyzed.

Results: A total of 1,542 unique ICU records were identified in the MIMIC-III database, among which 163 belonged to the dexmedetomidine group and 531 belonged to the midazolam group and 848 belonged to the propofol group. Mortality was decreased in dexmedetomidine group compared with midazolam group (OR 15.25; 95% CI, 5.29–64.80, $P < 0.001$) and propofol group (OR 5.51; 95% CI, 1.91–23.45, $P = 0.006$). In patients with high Simplified Acute Physiologic Score (SAPS) II (> 52), midazolam was related to a higher mortality (~50%). But competing risk analysis revealed that dexmedetomidine was associated with longer ICU stay ($P < 0.001$). There was no significant difference in the RASS between propofol and midazolam group ($P = 0.300$).

Conclusions: Dexmedetomidine was significantly related to lower mortality when compared with midazolam and propofol. Midazolam had a comparably higher mortality than propofol and dexmedetomidine in patients with high SAPS II. Propofol and midazolam were equivalent in sedative efficacy. Further evaluation is needed.

Keywords: Dexmedetomidine; midazolam; MIMIC-III database; mortality; propensity score matching (PSM); propofol

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Introduction

Patients in the intensive care units (ICU) are usually treated with many invasive therapies such as mechanical ventilation (MV), which may cause anxiety and discomfort. Actually, nonnegligible factors such as pain, delirium as well as oversedation have an effect on prognosis (1). Therefore, sedation is essential for ICU patients to facilitate tolerance of MV, reduce agitation, enhance comfort and reduce metabolic demands (2).

Midazolam, a gamma-aminobutyric acid (GABA) agonist, is a traditional sedative for ICU patients. Its advantages include that either continuous or intermittent administration are acceptable and a short duration of effect. However, continuously infusion and a high dose of midazolam may increase the risk of delirium and respiratory depression (3,4). Propofol is also a preferred sedative for ICU patients because of its short duration of effect and quick onset. Dexmedetomidine, a highly selective alpha-2 receptor agonist target at the locus coeruleus, provides an alternative to GABA agonist for ICU sedation (5). The benefits of dexmedetomidine for ICU patients are inconclusive. Studies suggest that dexmedetomidine reduced duration of MV compared to other sedatives but did not improve length of hospital stay and length of ICU stay (6,7).

Long stay in the ICU adds to the burden of health care costs and can be considered an indicator for efficiency of health care resource utilization, thus more evidence is needed to guide the sedative medication for ICU patients (8,9). Our study compared dexmedetomidine with propofol and midazolam using data from the Medical Information Mart for Intensive Care III (MIMIC-III) database. The effects of these three drugs on mortality, length of hospital stay, length of ICU stay, duration of MV, and sedation efficiency were explored.

Methods

Clinical database

The MIMIC-III database is a large and freely available database comprising more than 40,000 patients in the ICU of the Beth Israel Deaconess Medical Center in Boston, MA, USA between 2001 and 2012. De-identified data including lab results, electronic documentation, bedside monitor trends and waveforms are available (10). This study used a public de-identified database thus informed consent and approval of the Institutional Review Board was waived.

Our access to the database was approved after completion of the Collaborative Institutional Training Initiative (CITI program) web-based training course called “Data or Specimens Only research” (Record ID: 22861401).

Data extraction

Subjects who were continuously given dexmedetomidine, midazolam or propofol exclusively as sedative by intravenous infusion for more than 24 hours but less than 100 hours were identified from the database. Patients with other administration routes like intravenous injection and intramuscular injection were excluded. Another exclusion criterion was an age beyond the range of 18 to 90.

Demographic information collected at admission such as age, gender and primary diagnosis was extracted from the database. We simplified the diagnoses by clustering similar primary diagnoses according to the Clinical Classifications Software suggested by Agency for Healthcare Research and Quality (AHRQ) (11). Then we classified the diagnoses into different system categories such as circulation, respiration, renal according to respective organs involved. Mortality and dynamic physiological measurements such as Simplified Acute Physiologic Score (SAPS) II evaluated at ICU admission were also extracted from the MIMIC-III database directly (12). Overall infusion time of each sedative was computed by summing every discontinuous infusion fragment, which was defined as duration between end time and start time. Length of ICU stay was defined as duration between date of discharge or transferring or death and admission date. The duration of ventilation was calculated by counting any ventilator setting and ending records. If a single patient had multiple ventilation records, only those during which sedative was used for more than 6 hours were counted. Patients without ventilation records were also included in the analysis.

Patients on any vasopressor/inotrope (norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, dobutamine, milrinone) during ICU stay were considered hemodynamically unstable. Similarly, use of neuromuscular blocking agents [NMBA, e.g., (Cis)Atracurium, Rocuronium, Vecuronium, Pancuronium and Atracurium] was also considered a confounding factor for mortality since patients who required them were in more severe conditions and had higher risk of mortality.

Richmond Agitation-Sedation Score (RASS or RAS Score) is a commonly used scoring system to assess the depth of sedation (13). All RASS records of sedated patients

were collected from the MIMIC-III database. However, not all sedated patients had RASS due to a considerable amount of missing data, especially patients in the dexmedetomidine group. Thus, only the RASS of midazolam and propofol groups would be compared.

Some patients were admitted to ICU for several times and their records related to each time of admission were included in our study separately in order to make the most of data. These cases were marked as repeated so their influences and possible bias could be under control in further analysis.

Outcomes

The primary outcome was ICU mortality. The secondary outcomes included length of ICU stay and RASS. As a competing risk event, in-ICU death might shorten length of ICU stay. Therefore, competing risk analysis was performed for the comparison of length of ICU stay between each group.

Statistical analysis

Firstly, we summarized the baseline data of included patients, who were grouped by the sedative they used. Features of the three groups were compared to evaluate the data's heterogeneity. Then, the data was fitted with a logistic regression model to find out independent risk factors for ICU death. Furthermore, stratified analysis was performed according to the risk factors identified in the logistic regression. Box-plots were used to visualize the results of stratified analysis. At last, propensity score matching (PSM) was applied to balance the confounding factors that influenced sedative efficacy and create comparable units of midazolam and propofol patients. Covariates included age, gender, infusion time, SAPS II. Matching ratio was set as 1:1 and nearest neighbor matching method was used. The comparison of RASS between midazolam and propofol groups after PSM were visualized in a box-plot.

Categorical variables were expressed as the number and percentage, and their differences among groups were compared using Chi-squared test. Noncontinuous variables and continuous variables that didn't follow normal distribution were expressed as median and quartiles, and were analyzed with non-parametric methods (Mann-Whitney-Wilcoxon for two groups, Kruskal-Wallis for multi-groups). Continuous variables that followed normal distribution were expressed as mean and standard deviations,

and *t*-test (two groups) or Analysis of Variance (ANOVA) (multiple groups) was used for these variables. We used PostgreSQL 9.5 to construct the MIMIC-III database locally. All analyses were performed with R language 3.4.2. MatchIt package was used for PSM and ggplot2 packages was used for data visualization (14,15). A *P* value <0.05 was considered statistically significant.

Results

After screening the database according to the inclusion and exclusion criteria, a total of 1,542 unique ICU records were identified in the MIMIC-III database, among which 163 belonged to the dexmedetomidine group and 531 belonged to the midazolam group and 848 for propofol (*Figure 1*). Median and quartile infusion doses were 0.4 (0.3–0.6) mcg/kg/h for dexmedetomidine, 2.0 (1.0–4.0) mg/h for midazolam and 40 (28–55 mcg/kg/min) for propofol. The baseline information of each group was summarized in *Table 1*. The three groups were highly heterogeneous in almost every feature.

Analysis of the data revealed that patients who were given midazolam had the highest ICU mortality (dexmedetomidine: 1.8%, midazolam: 35.0%, propofol: 11.0%, *P*<0.001). The dexmedetomidine group had the longest length of ICU stay [dexmedetomidine: 10.27 (5.90, 17.47) d, midazolam: 4.35 (3.03, 6.45) d, propofol: 4.21 (2.98, 6.14) d, *P*<0.001] as well as ventilation duration [dexmedetomidine: 111.46 (61.80, 195.30) h, midazolam: 57.50 (37.08, 86.17) h, propofol: 46.28 (32.68, 71.00) h, *P*<0.001]. In addition, up to a half of patients with circulation system diseases were given dexmedetomidine as sedative (49.7%). And patients with respiratory diseases were more likely to be given midazolam (48.4%).

The multivariate analysis of logistic regression show similar results that dexmedetomidine was associated with a lower mortality compared with midazolam (OR 15.25; 95% CI, 5.29–64.80, *P*<0.001) and propofol (OR 5.51; 95% CI, 1.91–23.45, *P*=0.006) (*Table 2*). Besides drugs, infusion time, SAPS II, diagnoses, vasopressor use and NMBA use were also independent risk factors for in-hospital death of the ICU patients. One score elevation in SAPS II would increase the risk of death by 1.05 times (OR 1.05; 95% CI, 1.04–1.06, *P*<0.001). Similarly, one more hour of sedatives infusion would increase the risk of death by 1.01 times [1.01 (1.00–1.02), *P*=0.002]. What's more, patients that used any vasopressor as well as NMBA had a higher risk of death compared with others (OR 3.84; 95% CI, 2.61–5.75) for vasopressor and 3.71 (2.30–6.00) for NMBA, *P*<0.001 for

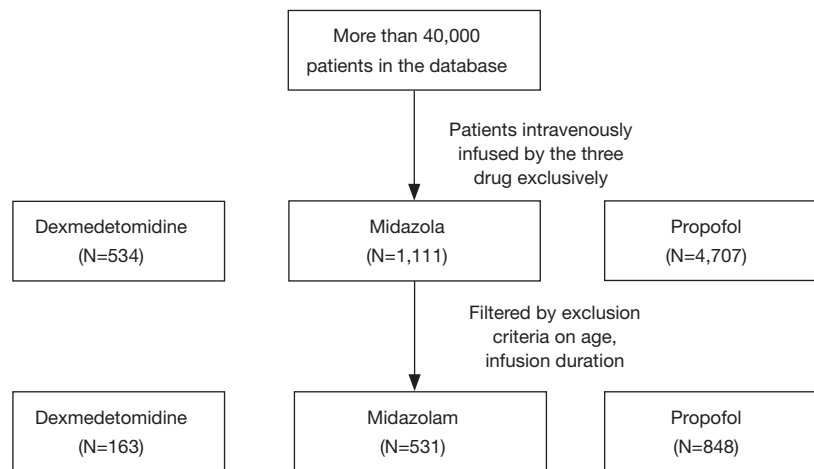


Figure 1 Flow plot of data extraction and filtration from the MIMIC-III database.

Table 1 Baseline data of included patients grouped by drugs

Features	Dexmedetomidine	Midazolam	Propofol	P value
No.	163	531	848	
Age (years) [mean (SD)]	59.16 (17.08)	66.25 (14.37)	61.30 (16.55)	<0.001 ^a
Gender (female/male) (%)	34/129 (20.9/79.1)	226/305 (42.6/57.4)	348/500 (41.0/59.0)	<0.001
Length of ICU stays (d) [median (IQR)]	10.27 [5.90, 17.47]	4.35 [3.03, 6.45]	4.21 [2.98, 6.14]	<0.001 ^b
Infusion time (h) [median (IQR)]	43.25 [30.88, 55.12]	46.98 [34.88, 65.87]	43.01 [32.55, 61.59]	0.007 ^b
SAPS II [median (IQR)]	35.00 [27.00, 42.50]	47.00 [37.00, 58.00]	37.00 [30.00, 48.00]	<0.001 ^b
Ventilation patients number (%)	155 (95.1)	504 (94.9)	847 (99.9)	<0.001
Ventilation duration (h) [median (IQR)]	111.46 [61.80, 195.30]	57.50 [37.08, 86.17]	46.28 [32.68, 71.00]	<0.001 ^b
Repeated ICU stay (%)	0 (0.0)	13 (2.4)	40 (4.7)	0.001 ^c
Vasopressor use (%)	112 (68.7)	366 (68.9)	353 (41.6)	<0.001
NMBA use (%)	17 (10.4)	62 (11.7)	52 (6.1)	0.001
No. of ICU death (%)	3 (1.8)	186 (35.0)	93 (11.0)	<0.001 ^c
Diagnoses category (%)				<0.001 ^c
Circulation	81 (49.7)	61 (11.5)	113 (13.3)	
CNS	4 (2.5)	14 (2.6)	137 (16.2)	
Diabetes	1 (0.6)	4 (0.8)	6 (0.7)	
Liver	2 (1.2)	18 (3.4)	33 (3.9)	
Renal	1 (0.6)	10 (1.9)	9 (1.1)	
Respiratory	15 (9.2)	257 (48.4)	131 (15.4)	
Trauma	24 (14.7)	19 (3.6)	148 (17.5)	
Other	35 (21.5)	148 (27.9)	271 (32.0)	

^a, tested by parametric method (ANOVA); ^b, tested by non-parametric method (Kruskal-Wallis); ^c, tested by Fisher's exact method. SAPS II, Simplified Acute Physiologic Score II; CNS, central neural system; SD, standard deviation; IQR, interquartile range; NMBA, neuromuscular blocking agents.

Table 2 Multivariate analysis of risk factors for in-ICU death

Features	OR (95% CIs)	P value
Age	1.00 (0.99–1.02)	0.455
Gender (male)	1.20 (0.87–1.66)	0.265
Infusion time	1.01 (1.00–1.02)	0.002**
SAPS II	1.05 (1.04–1.06)	<0.001***
Ventilation (yes)	–	0.971
Repeat ICU stay	0.33 (0.09–0.95)	0.059
Vasopressor use	3.84 (2.61–5.75)	<0.001***
NMBA use	3.71 (2.30–6.00)	<0.001***
Drugs		
Dexmedetomidine	1	
Midazolam	15.25 (5.29–64.80)	<0.001***
Propofol	5.51 (1.91–23.45)	0.006**
Diagnoses		
Circulation	1	
CNS	7.20 (3.62–14.54)	<0.001**
Diabetes	6.45 (1.05–34.96)	0.034*
Liver	1.34 (0.47–3.58)	0.559
Renal	1.70 (0.45–5.80)	0.407
Respiratory	2.53 (1.47–4.44)	<0.001***
Trauma	3.35 (1.62–6.91)	0.001**
Other	2.14 (1.21–3.84)	0.009**

*, P<0.05; **, P<0.01; ***, P<0.001. SAPS II, Simplified Acute Physiologic Score II; CNS, central neural system; OR, odds ratio; Cis, confidential intervals; NMBA, neuromuscular blocking agents.

both). And patients with central neural system (CNS) and respiratory diseases would have an extremely higher risk of death compared with patients with circulation system diseases [7.20 (3.62–14.54) for CNS and 2.53 (1.47–4.44) for respiratory, P<0.001 for both].

Based on the analyses above, further analysis was performed with patients stratified into several categories according to SAPS II and diagnoses. SAPS II was divided into 4 quarters according to the quartiles (*Figures 2,3A*). Dexmedetomidine group had the lowest mortality in all four SAPS II quarters. As the SAPS II rose (especially in quarter 3 and quarter 4), patients in the midazolam group had an extremely high mortality rate.

Stratified analyses were also performed in survivors to compare the secondary outcomes. Generally,

dexmedetomidine had the longest length of ICU stay in most of the SAPS II quarters and diagnosis groups. Midazolam group and propofol group didn't show significant differences (*Figure 3A*). The competing risk analysis suggested that despite the competing effects of in-ICU death, dexmedetomidine still show a longer ICU stay (P<0.001), especially in the first 10 days (*Figure 3B*).

Only 3 patients in dexmedetomidine group had RASS records during sedative infusion. There were few missing data in other groups that 322 patients in midazolam group and 520 patients in propofol group had records of RASS during sedative infusion. Thus, only the sedative efficacy of midazolam and propofol were compared after PSM (*Table 3, Figure 4*). PSM created compared units of midazolam and propofol groups where potential

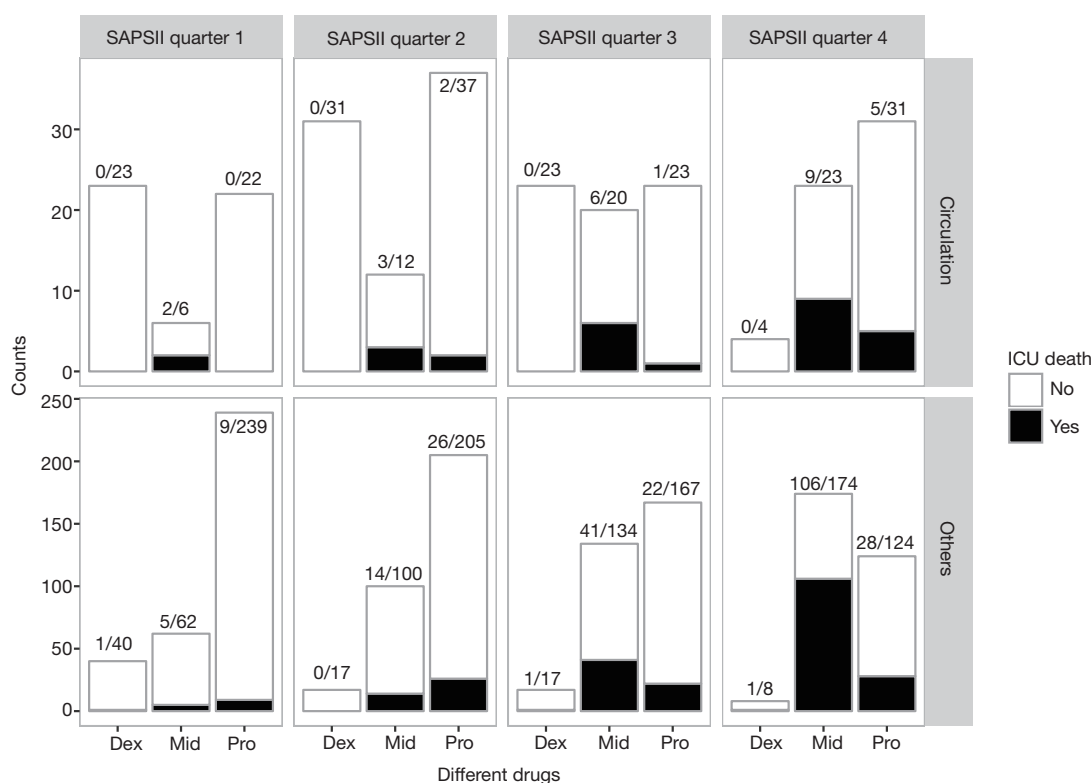


Figure 2 The stratified analysis of mortality among three groups. The columns indicated the number of cases, black for the dead and white for survivals. The numbers on top of bars present the dead numbers over total numbers. SAPS, Simplified Acute Physiologic Score; Dex, dexmedetomidine; Mid, midazolam; Pro, propofol.

confounding factor such as age, gender, infusion duration and SAPS II were homogeneous and sedative efficacy became comparable. And the result showed that there was no significant difference in sedative efficacy between midazolam and propofol ($P=0.300$) (Figure 5).

Discussion

Our study revealed that dexmedetomidine was significantly associated with lower mortality and increased length of ICU stay compared to propofol and midazolam. Moreover, ICU patients with propofol and midazolam infusions might achieve a similar depth of sedation level with a similar RAS score.

Mortality in the dexmedetomidine group was lower than that in the propofol and midazolam group, which was supported by both univariate and multivariate analyses. The findings of our study lacked strong convincing power because of the limitations of retrospective design. However, our conclusions were supported by other studies (16,17).

The decreased mortality of dexmedetomidine group may be attributed to the following factors. Unlike midazolam and propofol, dexmedetomidine provides arousable sedation, in which patients can cooperate and communicate with healthcare providers and avoid over sedation (5). And it is reported that dexmedetomidine improved the sleep quality and modified sleep patterns in critically ill patients (18).

Our study revealed that midazolam was associated with high mortality and most of death cases had high SAPS II, which indicated a more severe illness. In cases that SAPS II was higher than 52 (Quarter 4), the mortality of midazolam group exceeded 50%. Similar results were reported in previous studies. A multicenter ICU database analysis including more than 3,000 patients reported that continuous midazolam infusion was associated with a higher mortality (risk ratio 1.32) and lower likelihood of earlier ICU discharge than propofol (19).

Although its benefits on mortality was confirmed in our study, dexmedetomidine unexpectedly increased that length of ICU stay compared with midazolam and

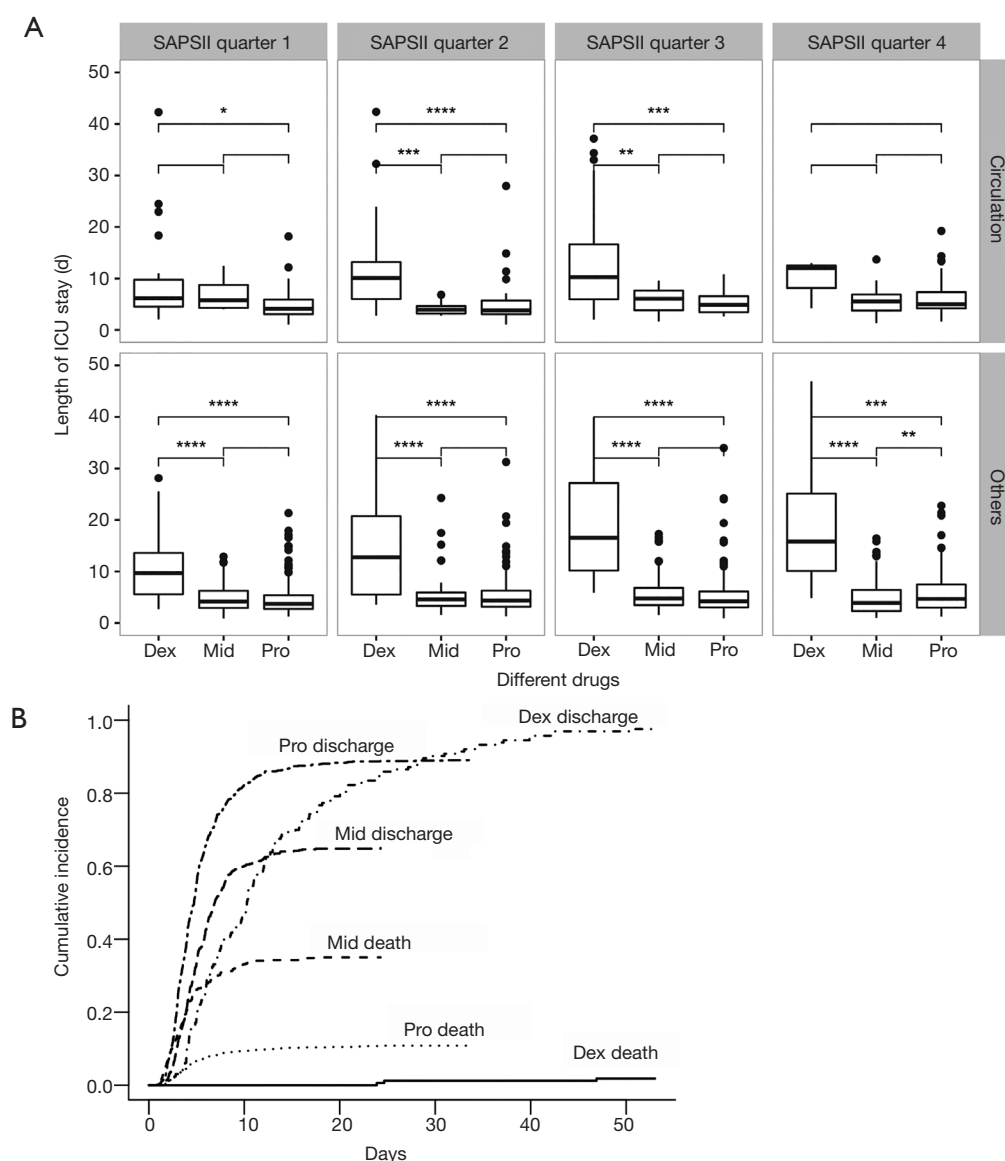


Figure 3 The analyses of length of ICU stay for three sedatives. (A) The stratified analysis: the SAPSII were divided into quartiles (Quarter 1, 0–30; Quarter 2, 31–40; Quarter 3, 41–52; Quarter 4, 53–101). Others meant the diagnosis was not circulation associative. The P value in the top of each facet was for all three groups. The asterisks below over the brackets refers to P values less than 0.05 between every two groups (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$); (B) the competing risk analysis: discharge from ICU was defined as end event and death in ICU was the competing risk. SAPS, Simplified Acute Physiologic Score; Dex, dexmedetomidine; Mid, midazolam; Pro, propofol.

propofol. Since death might shorten the length of ICU stay, known as a competing effect, the competing risk analysis was performed. Nevertheless, the results still suggested that patients using dexmedetomidine stayed longer in ICU. Several factors might exert complex impact on length of ICU stay, such as nutritional status and family

support, which were not considered in our study because of missing or unquantifiable data (20). In addition, choice effects of medical decider might also have an unignorable contribution. Some studies reported that dexmedetomidine might reduce the economic costs (21,22). Therefore, Patients who had a long stay in hospital might be more

Table 3 Selected data relation to Richmond Agitation-Sedation Score before and after PSM

Features	Before PSM			After PSM		
	Midazolam	Propofol	P value	Midazolam	Propofol	P value
No.	322	520		322	322	
Age (years) [mean (SD)]	66.04 (14.43)	61.44 (17.08)	<0.001 ^a	66.04 (14.43)	65.79 (15.54)	0.834 ^a
Gender (female/male) (%)	139/183 (43.2/56.8)	223/297 (42.9/56.8)	0.993	139/183 (43.2/56.8)	146/176 (45.3/54.7)	0.634
Infusion time (h) [median (IQR)]	47.92 [35.22, 66.42]	43.89 [33.31, 63.38]	0.061 ^b	47.92 [35.22, 66.42]	46.31 [34.09, 65.26]	0.563 ^b
SAPSII [median (IQR)]	46.00 [36.00, 57.00]	37.00 [30.00, 47.00]	<0.001 ^b	46.00 [36.00, 57.00]	44.00 [36.00, 54.00]	0.071 ^b

^a, tested by parametric method (*t*-test); ^b, tested by non-parametric method (Mann-Whitney-Wilcoxon). SAPS II, Simplified Acute Physiologic Score II; IQR, interquartile range; SD, standard deviation; PSM, propensity score matching.

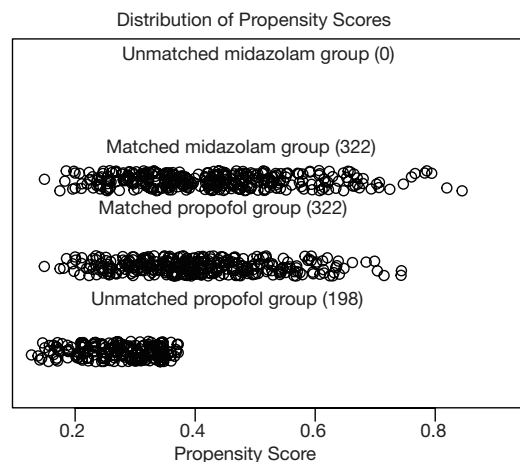


Figure 4 Distribution of Propensity Scores in matching process. The round points referred to cases, whose count is in brackets above. The X axis indicated the propensity score for every case.

likely to use dexmedetomidine to reduce costs. However, other studies had results opposite to our study. A meta-analysis done by Chen *et al.* revealed that dexmedetomidine reduced the length of ICU stay by 14% (95% CI, 1% to 24%; five studies, 1,223 participants, very low-quality evidence) (23). But there were also studies supporting our results. In an analysis carried out in an academic medical center, dexmedetomidine use was associated with increased lengths of ICU and hospital stay (21). These disparities in results indicate that more qualified research is needed.

The SAPS II is a method to evaluate the severity of the patients' illness. The characters considered in this scoring system include age, vital signs, admission type, and multi-

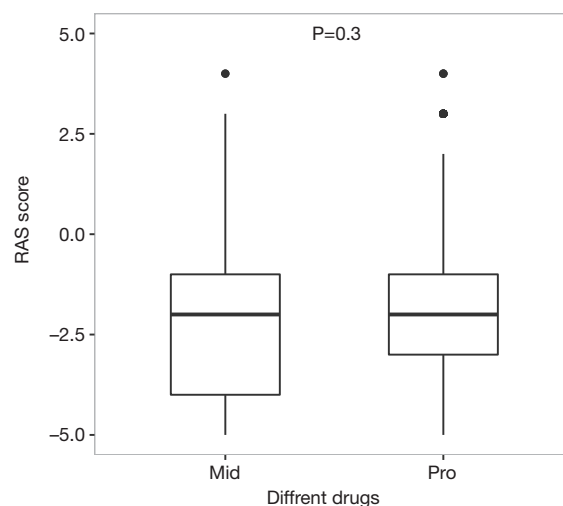


Figure 5 The boxplot of RAS Score for midazolam and propofol groups after propensity score matching. RAS, Richmond Agitation-Sedation; Mid, midazolam; Pro, propofol.

organ functions. In our logistic regression, SAPS II showed an extremely strong relation with ICU mortality (OR 1.05; 95% CI, 1.04–1.06, $P < 0.001$), indicating its powerful ability to predict outcomes. However, the association between age and mortality lacked statistical significance, which could be explained by the collinearity with SAPS II.

The dexmedetomidine patients had few records of RASS, which might attribute to the light and arousable sedation of dexmedetomidine. With a longer time at target sedation, dexmedetomidine was found to be noninferior to midazolam and propofol in light sedation (RASS 0 to -3) in a random trial done by Jakob *et al.* (6). However, Jakob

et al. found that the time at target sedation significantly decreased in dexmedetomidine patients when deep sedation was required (RASS -4 to -5) in their pilot study (7). Due to the limited data size, we did not analyze the sedation efficacy of dexmedetomidine and focused on other two forceful sedatives, midazolam and propofol. PSM is a powerful method to compare unbalanced groups. In our study, we chose age, gender, SAPS II and infusion time as confounding factors to perform the matching. And we found a similar sedative efficacy between these two sedatives, as other researches did (24,25).

In this retrospective study, we analyzed data from the MIMIC-III, a database containing information about tens of thousands of ICU patients, and applied PSM methods to reduce bias. Some limitations exist in our study. Firstly, the retrospective study revealed an association rather than causal relationship. Secondly, the missing data in RASS made it impossible to evaluate sedation efficacy of dexmedetomidine. At last, many factors inevitably introduced bias into the analysis of length of ICU stays, which might complicate the analysis and made the results inconclusive.

Conclusions

Dexmedetomidine was significantly related to lower mortality when compared with midazolam and propofol. However, its benefits on length of ICU stay was unproven. At the same time, midazolam had a relatively higher mortality than propofol and dexmedetomidine in patients with high SAPS II. Propofol and midazolam had similar sedative efficacy. Further evaluation is needed.

Acknowledgements

The datasets generated and/or analysed during the current study are available in the MIMIC-III v1.4, (<https://mimic.physionet.org>). The authors appreciate the efforts of the Medical Information Mart for Intensive Care III Database. Thanks to the researchers at the MIT Laboratory for Computational Physiology and collaborating research groups.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med* 2014;370:444-54.
2. Sydow M, Neumann P. Sedation for the critically ill. *Intensive Care Med* 1999;25:634-6.
3. Forster A, Gardaz JP, Suter PM, et al. Respiratory depression by midazolam and diazepam. *Anesthesiology* 1980;53:494-7.
4. Zaal IJ, Devlin JW, Hazelbag M, et al. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med* 2015;41:2130-7.
5. Gertler R, Brown HC, Mitchell DH, et al. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)* 2001;14:13-21.
6. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;307:1151-60.
7. Ruokonen E, Parviainen I, Jakob SM, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. *Intensive Care Med* 2009;35:282-90.
8. González-Cortés R, López-Herce-Cid J, García-Figueroa A, et al. Prolonged stay in pediatric intensive care units: mortality and healthcare resource consumption. *Med Intensiva* 2011;35:417-23.
9. Mamoli A, Censori B, Casto L, et al. An analysis of the costs of ischemic stroke in an Italian stroke unit. *Neurology* 1999;53:112-6.
10. Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data* 2016;3:160035.
11. Cowen ME, Dusseau DJ, Toth BG, et al. Casemix adjustment of managed care claims data using the clinical classification for health policy research method. *Med Care* 1998;36:1108-13.
12. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957-63.
13. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338-44.
14. Ho DE, Imai K, King G, et al. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. *Journal of Statistical Software* 2011;42:1-28.
15. Wickham H. Ggplot2: elegant graphics for data analysis.

- Use R! New York: Springer, 2009.
16. Ji F, Li Z, Nguyen H, et al. Perioperative dexmedetomidine improves outcomes of cardiac surgery. *Circulation* 2013;127:1576-84.
 17. Ji F, Li Z, Young N, et al. Perioperative dexmedetomidine improves mortality in patients undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2014;28:267-73.
 18. Alexopoulou C, Kondili E, Diamantaki E, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. *Anesthesiology* 2014;121:801-7.
 19. Lonardo NW, Mone MC, Nirula R, et al. Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. *Am J Respir Crit Care Med* 2014;189:1383-94.
 20. Awad A, Bader-El-Den M, McNicholas J. Patient length of stay and mortality prediction: A survey. *Health Serv Manage Res* 2017;30:105-20.
 21. Patanwala AE, Erstad BL. Comparison of Dexmedetomidine Versus Propofol on Hospital Costs and Length of Stay. *J Intensive Care Med* 2016;31:466-70.
 22. Turunen H, Jakob SM, Ruokonen E, et al. Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: an economic evaluation. *Crit Care* 2015;19:67.
 23. Chen K, Lu Z, Xin YC, et al. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev* 2015;1:CD010269.
 24. Guintier JR, Kristeller JL. Prolonged infusions of dexmedetomidine in critically ill patients. *Am J Health Syst Pharm* 2010;67:1246-53.
 25. McKeage K, Perry CM. Propofol: a review of its use in intensive care sedation of adults. *CNS Drugs* 2003;17:235-72.

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