

Renal Outcomes in Critically Ill Patients Receiving Propofol or Midazolam

Tacyano Tavares Leite,* Etienne Macedo,[†] Izanio da Silva Martins,* Fernanda Macedo de Oliveira Neves,* and Alexandre Braga Libório*

Abstract

Background and objectives Propofol has been shown to provide protection against renal ischemia/reperfusion injury experimentally, but clinical evidence is limited to patients undergoing cardiac surgery. There are no data about its association with oliguria and AKI in critically ill patients.

Design, setting, participants, & measurements We obtained data from the Multiparameter Intelligent Monitoring in Intensive Care II database (2001–2008). Patient selection criteria included adult patients in their first intensive care unit (ICU) admission, need for mechanical ventilation, and treatment with propofol or midazolam. Propensity score analysis (1:1) was used and renal-related outcomes (AKI, oliguria, cumulative fluid balance, and need for RRT) were evaluated during the first 7 days of ICU stay.

Results There were 1396 propofol/midazolam-matched patients. AKI in the first 7-day ICU time period was statistically lower in propofol-treated patients compared with midazolam-treated patients (55.0% versus 67.3%, $P<0.001$). Propofol was associated with lower AKI incidence using both urine output (45.0% versus 55.7%, $P<0.001$) and serum creatinine criteria (28.8% versus 37.2%, $P=0.001$). Patients receiving propofol had oliguria (<400 ml/d) less frequently (12.4% versus 19.6%, $P=0.001$) and had diuretics prescribed less often (8.5% versus 14.3%, $P=0.001$). In addition, during the first 7 days of ICU stay, patients receiving propofol less frequently achieved cumulative fluid balance >5% of body weight (50.1% versus 58.3%, $P=0.01$). The need for RRT in the first 7 days of ICU stay was also less frequent in propofol-treated patients (3.4% versus 5.9%, $P=0.03$). ICU mortality was lower in propofol-treated patients (14.6% versus 29.7%, $P<0.001$).

Conclusions In this large, propensity-matched ICU population, patients treated with propofol had a lower risk of AKI, fluid-related complications, and need for RRT.

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Introduction

AKI is now recognized as a major public health problem, affecting millions of patients worldwide (1). Critically ill patients are at high risk of developing AKI, with its incidence during intensive care unit (ICU) stay varying from 36% to 67% using the recent AKI definition (2,3). Its occurrence puts critically ill patients at increased risk of prolonged ICU stay, morbidity, and mortality. In addition, AKI has been associated with increased progression, or new onset, of CKD. Critically ill patients are exposed to several kidney insults (sepsis, ischemia, low cardiac output, drug nephrotoxicity, and underlying comorbidities). The underlying mechanisms involved in the pathogenesis of AKI in critically ill patients are multifactorial and not completely understood. Apart from patient-related factors, AKI is generally associated with proinflammatory changes (4).

Critically ill patients are frequently managed using a continuous-infusion sedative for comfort and to reduce anxiety. The sedation strategy in the ICU can include either benzodiazepine or nonbenzodiazepine

agents. In a meta-analysis (5), propofol was associated with shorter dependence on mechanical ventilation and ICU length of stay (LOS). Moreover, a recent larger retrospective study has shown that propofol was associated with better ICU survival compared with benzodiazepine sedation (6).

In addition to its intrinsic anesthetic properties, propofol has anti-inflammatory and immunomodulatory properties (7). Several animal studies suggested that propofol is effective in attenuating AKI in different models (8–10). Although it is commonly observed that therapeutic and preventive strategies related to AKI are successful in animal models and fail in human trials, a recent randomized controlled study showed that propofol anesthesia was associated with a reduction in AKI incidence in patients undergoing valvular heart surgery compared with sevoflurane anesthesia (11). Although these findings are intriguing, our enthusiasm is limited by the small number of patients involved and conflicting results with similar previous small trials also testing propofol. Moreover, the specific patient population used in

*Medical Sciences Postgraduate Program, Department of Clinical Medicine, Federal University of Ceará, Fortaleza-Ceará, Brazil; and [†]Department of Nephrology, Clinical Hospital, University of São Paulo, São Paulo, Brazil

Correspondence:

Dr. Alexandre Braga Libório, Medical Sciences Postgraduate Program, Department of Clinical Medicine, Federal University of Ceará, Avenida Abolição, 4043 Ap 1203, Fortaleza-Ceará, Brazil CEP 60165-082. Email: alexandreliborio@yahoo.com.br

this trial does not allow for generalization of the results to other surgical procedures or to critically ill patients overall.

On the basis of the potentially beneficial effects of propofol, we aim to evaluate the outcomes of patients receiving propofol exclusively during the first 48 hours of ICU stay compared with patients receiving midazolam. We hypothesized that propofol use could be associated with a decrease in the incidence and severity of AKI in critically ill patients.

Materials and Methods

Multiparameter Intelligent Monitoring in Intensive Care II Database and Data Collection

The Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-II) project, maintained by the Massachusetts Institute of Technology Laboratory for Computational Physiology, contains data on patients hospitalized in an ICU at Beth Israel Deaconess Medical Center from 2001 to 2008 (12). The database is freely available, so that any researcher who accepts the data use agreement and has attended “protecting human subjects training” can apply for permission to access the data. This study was approved by the institutional review boards of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center and was granted a waiver of informed consent.

We included all mechanically ventilated adult patients receiving propofol or midazolam for at least 6 hours during the first 48 hours after ICU admission. Patients with insufficient laboratory tests, those with known ESRD, and those who underwent RRT before ICU admission were excluded. In addition, patients with an ICU LOS <24 hours, individuals with admission serum creatinine >4 mg/dl, and those receiving both propofol and midazolam were excluded. The Supplemental Material provides a complete description of MIMIC-II and data collection.

AKI Definition

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Briefly, serum creatinine levels were used to classify AKI stage. Because our objective was to evaluate the effects of a sedative (propofol or midazolam) on renal function, the first serum creatinine measurement available after ICU admission was used as the reference for renal function. We classified patients based on the KDIGO maximum stage achieved during the first 7 days of ICU stay. Patients that received RRT during this period were considered as AKI stage 3. Urine output was assessed every hour. We used the urine output criterion for patients with at least 24 consecutive hours of valid output measurements. The KDIGO criterion was applied to those patients, calculating the weight-normalized urine output over a 6-hour period (13). In patients with insufficient urine output measurements, only the serum creatinine criterion was applied. To perform sensitivity analysis in a subgroup with normal renal function, we selected only patients with an eGFR >60 ml/min per 1.73 m² using the Modification of Diet in Renal Disease study formula. Moreover, we back-calculated baseline serum creatinine assuming a normal

baseline GFR of 75 ml/min per 1.73 m² and excluded patients that met the KDIGO criterion for serum creatinine at ICU admission.

Outcomes

Renal outcomes were assessed on the first 7 days of ICU stay, including maximum AKI stage by KDIGO using serum creatinine and urine output criteria, oliguria (<400 ml/d), diuretic use, cumulative fluid balance (calculated input and output fluids recorded as part of the nursing flow sheet), and RRT. The other secondary outcomes (ICU LOS and ICU mortality) were assessed after the entire ICU stay.

Statistical Analyses

Descriptive statistics was used initially, including means with SDs or frequencies, to describe the population as appropriate. For the univariate analysis, chi-squared tests and *t* tests were used to evaluate statistical significance. All tests were two sided, with *P*<0.05 considered significant. Propensity score matching techniques were then used to achieve balance of the measured baseline patient characteristics. Admission variables or those obtained during the first 48 hours of ICU stay were considered as identified as potential confounders and were used to build the initial logistic regression model to predict use of propofol. In addition, because AKI has been associated with mechanical ventilation in a bidirectional causality relationship and propofol has been associated with shorter mechanical ventilation duration, we included mechanical ventilation dependence after 48 hours and 7-day ICU time period in the propensity score matching. Model selection was performed using stepwise regression, retaining all covariates with *P*<0.20. This level of significance was chosen to ensure the inclusion of all variables that could influence the choice of propofol or midazolam administration. Covariates included sex, age, admission nonrenal Simplified Acute Physiology Score–I and Sequential Organ Failure Assessment scores, main comorbidities, ICU admission type (medical, surgical, or coronary), sepsis diagnosis, admission Glasgow Coma Scale score, renal function at ICU admission (first available serum creatinine measurement), need for vasoactive drugs during the first 48 hours of ICU stay, and median mean arterial blood pressure (MAP) in the first 48 hours of ICU stay. To match patients with similar propensity scores, 1:1 nearest-neighbor matching was utilized without replacements using a 0.1-SD caliper. Exact matching was not required for any of the variables. If no match was found, the propofol- or midazolam-treated patient was removed from the analysis (Supplemental Figures 1 and 2).

We assessed the degree of balance in measured covariates between the groups in the two studies (propofol versus midazolam) by comparing the distributions of categorical and continuous variables using chi-squared tests and *t* tests, respectively. Standardized differences, expressed as a percentage of the pooled SD of the covariates, were also used to assess prematching and postmatching balance of covariates; standardized differences of <0.1 indicate that covariates are well balanced between groups. After matching, further adjustment to explore the association between propofol use and renal

outcomes was performed for variables that remained with a $P < 0.20$.

We also performed a simulation-based sensitivity analysis to explore whether our results were prone to residual confounding using calculations in which we posited imbalanced unmeasured covariates of varying prognostic strength (14). The statistical analysis was performed using SPSS 19.0 for Windows.

Results

Population

The MIMIC-II database contains the records of 32,425 patients, 24,581 of which were individuals aged ≥ 15 years at the time of admission. In total, 1753 patients were excluded because of data on serum creatinine, another 3537 patients were excluded because their ICU LOS was < 24 hours, and another 538 patients were excluded because they had ESRD. Of the remaining patients, 9697 received propofol and/or midazolam in the first 48 hours after ICU admission. In addition, we further excluded 863 patients receiving both propofol and midazolam. Finally, a total sample of 8834 patients received propofol or midazolam in the first 48 hours of ICU stay (Figure 1). Propofol was the most commonly used sedative in this study population, comprising 91.7% of patients.

Before matching, patients receiving propofol were younger, had fewer comorbidities, and had lower serum creatinine at ICU admission. These differences are probably attributable to the different patient admission types: more than one-half of patients receiving propofol were surgical (cardiac or noncardiac) patients and 49% of patients receiving midazolam were medical admissions. A complete description of baseline variables for the unmatched cohort is described in Table 1.

Matched Cohort

After 1:1 matching for pretreatment variables, there were 698 propofol-treated patients matched to midazolam-treated patients (Table 1). All presedation demographic, clinical, and laboratory variables were well balanced between groups after propensity score matching, as shown in Table 1. Moreover, the successful narrowing of the standard difference of the covariates after propensity score matching for each comparison can be seen in Supplemental Figure 2. Thus, groups were rendered comparable regarding all of these covariates, and no further adjustment was required for the outcome analysis. In addition, exposition to other factors related to AKI (nephrotoxic drugs, volume infusion, and chloride-rich solutions) did not differentiate between the matched groups (see Table 1).

Propofol-treated patients received a mean infusion dose of $35.3 \mu\text{g}/\text{kg}$ per minute and the majority (79.0%) received propofol up to 72 hours of ICU stay. Regarding midazolam-treated patients, the mean dose was $0.8 \mu\text{g}/\text{kg}$ per minute and, as in the propofol group, the majority of patients had midazolam use interrupted before 72 hours of ICU stay (80.5%). During the first 7 days of ICU stay, there was no difference in the cumulative measurement of fentanyl (8.8 ± 3.3 mg versus 8.3 ± 3.4 mg, $P = 0.44$) and there were no differences in relation to morphine (16.7 ± 4.0 mg versus 19.1 ± 5.8 mg, $P = 0.73$).

AKI Development

Although some patients might have been admitted to the ICU with already established AKI, serum creatinine at admission was used as the baseline value to evaluate new or worsening AKI after propofol or midazolam treatment. After matching, propofol-treated patients had admission serum creatinine measurements were comparable to those of midazolam-treated patients. Only 176 patients (12.5%) were classified based only on serum creatinine (no significant difference between propofol- and midazolam-treated groups).

During the first 7 days of ICU stay, more midazolam-treated patients developed AKI (67.3% versus 55.0%, $P < 0.001$). There was a trend toward propofol-treated patients achieving maximum KDIGO AKI stage later after ICU admission, with a median 3 days (interquartile range [IQR], 2–5) versus 2 days (IQR, 2–4; $P = 0.07$). When considering both criteria (urine output and serum creatinine), propofol was associated with a significantly lower AKI incidence, with an odds ratio of 0.59 (95% confidence interval [95% CI], 0.48 to 0.74) (Table 2). The propofol-associated difference was observed in both urine output (OR, 0.65; 95% CI, 0.52 to 0.80) and serum creatinine KDIGO criteria (OR, 0.68; 95% CI, 0.54 to 0.85). A propofol-associated lower OR was observed in more severe AKI (stages 2 and 3) (Figure 2). As shown in Figure 3, propofol was associated with a lower incidence of AKI across the stages using either urine output or serum creatinine criteria.

Oliguria, Diuretic Use, and Cumulative Fluid Balance

Patients receiving propofol had oliguria (< 400 ml/d) less frequently (12.4% versus 19.6%, $P = 0.001$) and had diuretics prescribed less frequently (8.5% versus 14.2%, $P = 0.001$). The mean cumulative dose of furosemide during the first 7 days of ICU stay was higher in midazolam-treated patients (36.6 ± 18.1 mg versus 16.4 ± 9.8 mg, $P < 0.001$). In addition, during the first 7 days of ICU stay, patients receiving propofol less frequently achieved cumulative fluid balance $> 5\%$ of body weight (50.4 versus 58.4, $P = 0.003$). Complete data on the ORs related to these outcomes are shown in Table 2.

RRT

Taking only the first 7 days of ICU stay into consideration, there was a marginal but significantly lower RRT requirement associated with propofol treatment (3.4% versus 5.9%, $P = 0.03$; OR, 0.57; 95% CI, 0.34 to 0.95). Patients initiating RRT had oliguria (52.3%), serum bicarbonate < 18 mEq/L (69.1%), serum blood urea > 60 mg/dl (50.8%), and hyperkalemia (30.7%) as possible indications of RRT. The median time until RRT after ICU admission was 4 days (IQR, 2–5) (no difference between the groups).

Sensitivity Analyses for Renal-Related Outcomes

In the first sensitivity analysis, we excluded patients with previous CKD or AKI at ICU admission. The results remained the same for all outcomes, except for RRT, as shown in Table 3. A second sensitivity analysis was performed excluding patients who underwent cardiac surgery, with similar findings (Supplemental Table 1).

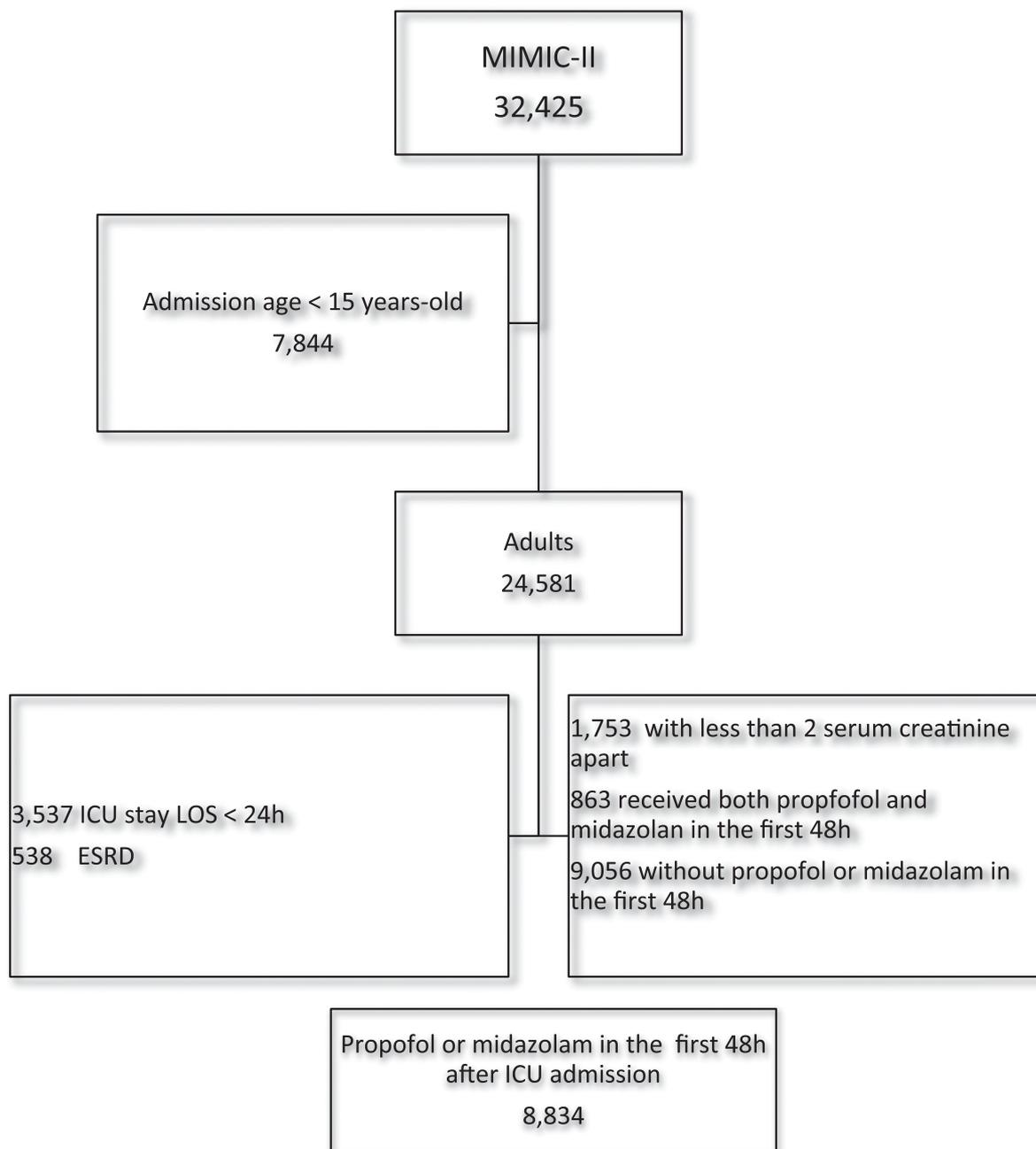


Figure 1. | Patient distribution in the MIMIC-II database and exclusion criteria. ICU, intensive care unit; LOS, length of stay; MIMIC, Multiparameter Intelligent Monitoring in Intensive Care.

Finally, although most known risk factors for AKI in critically ill patients were already assessed in propensity scoring matching, we also performed sensitivity to unmeasured confounding, first focusing on AKI development. To account for the reduction in the adjusted odds of AKI in the propofol-treated group, an unmeasured confounder that increased the odds of AKI by 60% would need to be present in 40% (*e.g.*, 10% versus 50% of patients) more midazolam-treated patients than patients receiving propofol. Conversely, if the imbalance were only 10%, the unmeasured confounder would need to increase the odds of AKI by 150%. Similar stronger or badly

imbalanced, unmeasured confounders must be posited to account for the associations of propofol use with oliguria and diuretic use.

For RRT, the sensitivity analysis disclosed that unmeasured confounders that increased the odds of RRT by 10% would need to be present in 40% more midazolam-treated patients to account for the reduction in OR.

ICU LOS and Mortality

In matched patients, there was a trend toward reduced ICU LOS in propofol-treated patients (8.2 ± 4.9 days versus

Table 1. Unmatched and matched covariates: Propofol versus midazolam

Variable	Unmatched Cohort			Matched Cohort		
	Propofol (n=8099)	Midazolam (n=735)	P Value	Propofol (n=698)	Midazolam (n=698)	P Value
Age (yr)	62.2±16.9	66.1±17.0	<0.001	65.5±16.5	66.0±17.2	0.55
Men	5099 (63.0)	395 (53.7)	<0.001	369 (52.9)	375 (53.7)	0.87
Hypertension	2425(29.9)	227 (30.9)	0.59	203 (29.1)	215 (30.8)	0.48
Diabetes mellitus	1597(19.7)	179 (24.4)	0.003	170 (24.4)	167 (23.9)	0.85
Congestive heart failure	1096 (13.5)	276 (37.6)	<0.001	252 (36.1)	258 (37.0)	0.74
COPD	1158 (14.3)	199 (27.1)	<0.001	169 (24.2)	185 (26.5)	0.33
Liver disease	339 (4.2)	57 (7.8)	<0.001	56 (8.0)	55 (7.9)	0.92
Solid tumors	1075 (13.3)	132 (18.0)	<0.001	128 (18.3)	123(17.6)	0.73
Neurologic conditions	217 (2.7)	50 (6.8)	<0.001	47 (6.7)	46 (6.6)	0.75
Obesity	186 (2.3)	17 (2.3)	0.98	15 (2.1)	17(2.4)	0.72
Emergency admission	3272 (40.4)	439 (59.7)	<0.001	359 (51.4)	372 (53.3)	0.52
ICU first service						
Medical	2321 (25.9)	366 (49.3)	<0.001	352 (50.4)	333 (47.7)	0.52
Surgical	4832 (54.0)	155 (20.9)		131 (18.8)	153 (21.9)	
Cardiac care	1244 (13.9)	207 (27.9)		200 (28.7)	197 (28.2)	
Cardiac surgery	557 (6.2)	15 (2.0)		15 (2.1)	15 (2.1)	
Sepsis	362 (4.0)	192 (25.8)	<0.001	129 (18.5)	153 (21.9)	0.11
SAPS on ICU admission	16 (13–19)	18 (15–21)	<0.001	17 (14–20)	17 (14–19)	0.35
Nonrenal SOFA on ICU admission	6.5±3.5	7.2±3.9	<0.001	7 (4–10)	7 (5–10)	0.34
Glasgow Coma Scale score	6 (3–10)	9 (6–14)	<0.001	7 (3–11)	8 (3–12)	0.30
Opioid agent	3065 (37.8)	577(78.5)	<0.001	555(79.5)	573(82.1)	0.25
MAP in the first 48 h (mmHg)	78.8±9.5	76.5±10.1	<0.001	77.4±9.6	76.7±10.1	0.33
Need for vasoactive drugs in the first 48 h	4139 (51.8)	309 (42.0)	<0.001	282 (40.4)	295 (42.3)	0.48
Serum creatinine at ICU admission (mg/dl)	0.8 (0.7–1.1)	1.2 (0.8–2.0)	<0.001	1.1 (0.8–1.7)	1.2 (0.8–1.9)	0.39
Use of nephrotoxic drugs						
Vancomycin	5175 (63.9)	607 (82.6)	<0.001	466 (66.8)	484 (69.3)	0.33
Aminoglycoside	259 (3.2)	43 (5.8)	0.001	53 (7.6)	37 (5.3)	0.08
Amphotericin	389 (4.9)	46 (6.3)	0.09	54 (7.7)	48 (6.9)	0.54
Contrast administration	1397 (17.2)	137 (18.6)	0.33	128 (18.3)	135 (19.3)	0.68
Volume infusion in the first 7 d of ICU (ml/d)	2179±1889	2415±1921	0.001	2132±1810	2196±1824	0.51
Chloride-rich solution infusion in the first 7 d of ICU stay (ml/d)	679±601	836±661	<0.001	638±606	669±507	0.30
Use of HES	148 (1.8)	18 (2.4)	0.25	14(2.0)	12 (1.7)	0.84
Dependence of mechanical ventilation			<0.001			0.24
48 h	2219 (27.4)	398 (54.1)		372 (53.3)	366 (52.4)	
7 d	1628 (20.1)	322 (42.8)		271 (38.7)	286 (41.0)	

Data are presented as mean ± SD, n (%), or median (interquartile range). COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; HES, hydroxyethyl starch.

9.1±5.3 days, $P=0.05$). ICU mortality was lower in propofol-treated patients (14.6% versus 29.7%, $P<0.001$).

Discussion

In this retrospective cohort study of mechanically ventilated, critically ill patients, we selected two matched populations treated with a single sedative in the first 48 hours of ICU stay. In this matched population, propofol was associated with statistically lower risk for developing AKI and several other important renal-related outcomes. The results of this propensity score analysis, which controlled for important pretreatment variables and for mechanical

ventilation dependence, are supported by previous animal studies and one small but important randomized clinical trial in patients undergoing valvular heart surgery (8,10,11).

Propofol is a widely used agent for the induction and maintenance of general anesthesia and for the sedation of critically ill patients. It has antioxidant and anti-inflammatory properties (7,15). Propofol treatment can inhibit proinflammatory cytokines in both animal models and patients with sepsis (7,16–18). The renal beneficial effects of propofol have been demonstrated in animal models using either ischemia/reperfusion (10) or sepsis injuries (8). Another proposed mechanism for the association of

Table 2. Outcome measures with matching cohorts

Outcome	Midazolam-Matched Cohort (n=698)	Propofol-Matched Cohort (n=698)	P Value	OR (95%CI)	Adjusted OR (95%CI) ^a
AKI (any stage)	470 (67.3)	384 (55.0)	<0.001	0.59 (0.48 to 0.74)	0.58 (0.48 to 0.72)
AKI stage 1	135 (19.3)	139 (19.9)		1.04 (0.80 to 1.35)	1.04 (0.80 to 1.36)
AKI stage 2	172 (24.6)	130 (18.6)	<0.001	0.70 (0.54 to 0.91)	0.68 (0.53 to 0.88)
AKI stage 3	163 (23.4)	115 (16.5)		0.65 (0.50 to 0.85)	0.65 (0.50 to 0.85)
Oliguria (<400 ml/d) ^b	123/627 (19.6)	73/591 (12.4)	0.001	0.57 (0.42 to 0.78)	0.58 (0.42 to 0.79)
Diuretic use	100 (14.3)	60 (8.5)	0.001	0.56 (0.40 to 0.79)	0.55 (0.39 to 0.78)
Cumulative fluid balance >5% body wt	407 (58.3)	350 (50.1)	0.01	0.73 (0.59 to 0.91)	0.72 (0.58 to 0.90)
RRT	41 (5.9)	24 (3.4)	0.03	0.57 (0.34 to 0.96)	0.57 (0.34 to 0.96)
ICU mortality	207 (29.7)	102 (14.6)	<0.001	0.40 (0.31 to 0.87)	0.40 (0.31 to 0.82)

Except for ICU mortality, all outcomes were considered in the first 7 days of intensive care unit stay. ICU, intensive care unit; OR, odds ratio; 95% CI, 95% confidence interval.

^aAdjusted for aminoglycoside and sepsis.

^bUrine output was accessible in 1218 patients (87.3%).

propofol with a lower risk of AKI is the increase in bone-morphogenetic protein-7 expression during sepsis-induced AKI in animals (8).

Although many drugs have shown potential benefits in AKI using animal models, none has shown clinical value in patients at high risk of developing AKI. Because its potential renoprotection is achieved using the recommended dosage used in sedation/anesthesia, propofol is emerging as an option with potential for use in clinical practice. However, the results of small clinical trials regarding AKI outcome are conflicting. Propofol was recently

associated with lower AKI incidence in patients undergoing valvular heart surgery (11). This was a randomized, well balanced, and well conducted study; however, the limited setting of clinical conditions (cardiac surgery), small number of patients, and a population with relatively few comorbidities limit our enthusiasm. Moreover, other studies have not shown any benefits with propofol (versus inhaled anesthetics) for AKI in the setting of cardiac surgery (19,20). In a study of patients with cirrhosis who underwent liver resection and were randomized to receive sevoflurane or propofol as the main anesthetic agent,

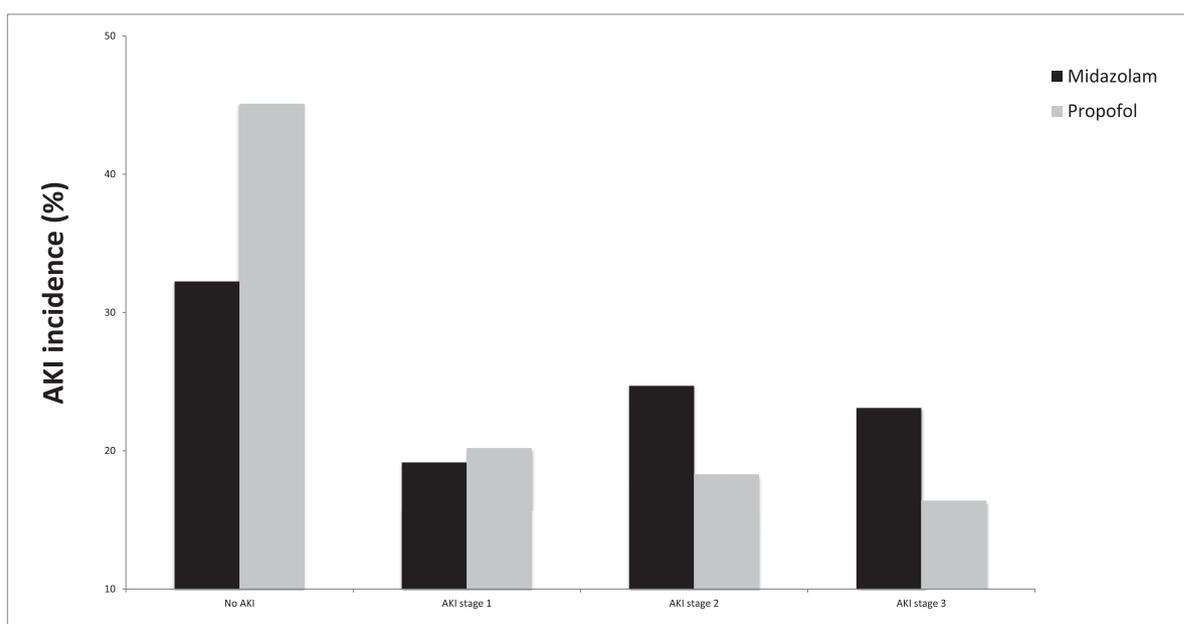


Figure 2. | AKI incidence in propofol- or midazolam-treated patients. AKI was classified through both serum creatinine measurement and urine output.

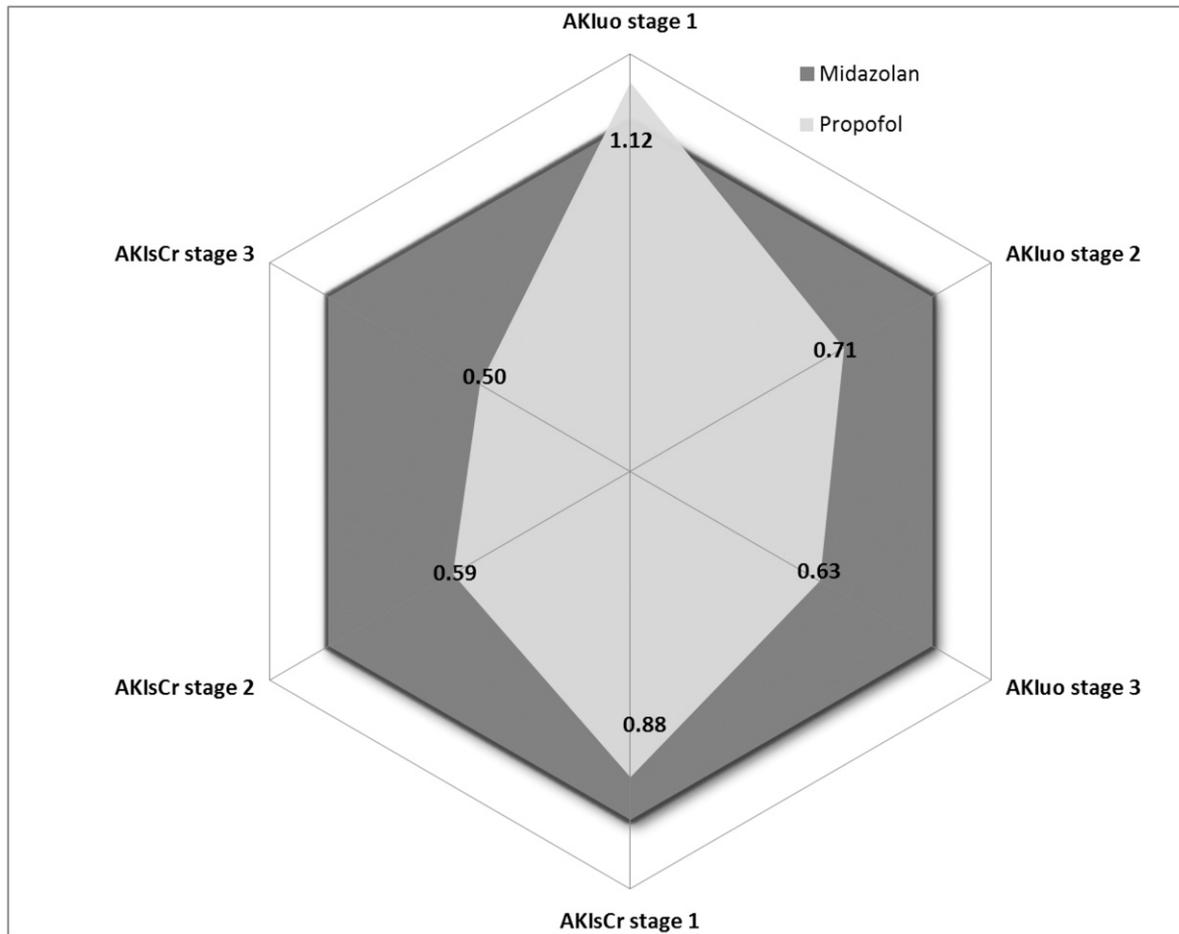


Figure 3. | Odds ratios for AKI according to AKI stage and classification criteria (urine output or serum creatinine). Observe that propofol was associated with a lower incidence of AKI in stages 2 and 3 with either the serum creatinine or urine output criterion. Midazolam-treated patients (dark gray zone) comprised the reference group. AKIsCr, AKI serum creatinine criterion; AKluo, AKI urine output criterion.

Song *et al.* (21) also found no difference in postoperative renal function. Extrapolating these results to general critically ill patients is troublesome, and we can thus affirm that the renal effects of propofol as a sedative agent in the ICU remain unknown.

In our study, we matched mechanically ventilated patients receiving propofol or midazolam in the first 48 hours of ICU stay. After matching, we had two highly comparable populations regarding their baseline characteristics. Not only did we use baseline patients' characteristics

Outcome	Midazolam-Matched Cohort (n=346)	Propofol-Matched Cohort (n=354)	P Value	OR (95%CI)
AKI stage 1	60 (17.3)	62 (17.5)		1.01 (0.69 to 1.48)
AKI stage 2	87 (25.1)	66 (18.6)	<0.001	0.68 (0.48 to 0.98)
AKI stage 3	59 (17.1)	30 (8.5)		0.45 (0.28 to 0.72)
Oliguria (<400 ml/d) ^a	42/319 (13.2)	14/334 (4.2)	<0.001	0.29 (0.15 to 0.54)
Diuretic use	43 (12.4)	25 (7.1)	0.01	0.54 (0.33 to 0.89)
Cumulative fluid balance >5% body wt	195 (56.3)	173 (48.9)	0.01	0.81 (0.69 to 0.95)
RRT	6 (1.7)	2 (0.6)	0.13	0.32 (0.06 to 1.61)
ICU mortality	69 (19.9)	32 (9.0)	<0.001	0.40 (0.25 to 0.63)

Except for ICU mortality, all outcomes were considered for the first 7 days of ICU stay. ICU, intensive care unit; OR, odds ratio; 95% CI, 95% confidence interval.
^aUrine output was accessible in 653 patients (93.3%).

and ICU admission features to match the patients, but we also included dynamic variables regarding patients' hemodynamic data (mean MAP and use of vasoactive drugs) during the first 48 hours of ICU stay that could interfere in the sedative choice. To exclude any late renal event during ICU stay that could not be associated with the initial sedation choice, we also limited the renal outcomes to the first 7 days of ICU stay. Notably, there was a reduction in all adverse renal outcomes studied, including need for RRT.

Because some patients were already admitted to ICU with established or ongoing AKI, we used the first serum creatinine measurement after ICU admission as the baseline value. By using this definition, we were certainly evaluating only new developed or worsening AKI cases after sedation was initiated. Propofol was associated with lower incidence of AKI mainly in its most severe stages (2 and 3) and the results were very similar when using either the serum creatinine or urine output criterion. Interestingly, higher cumulative fluid balance, another feature associated with higher ICU mortality, was less common in propofol-treated patients, even though these patients receiving diuretics less frequently. In this study, we preferred to use a lower cutoff than the one commonly used to define higher cumulative fluid balance (5% of body weight) because we evaluated only the first 7 days of ICU stay.

As stated above, other studies evaluating propofol effects on renal function were performed during surgery anesthesia. There are differences in propofol administration for sedation in critically ill patients or in anesthesia induction during surgery. First, the infusion rate in our cohort was only one-third of that used in the randomized trial performed by Yoo *et al.* (11) during valvular heart surgery. However, this low infusion rate can be counterbalanced by the more prolonged infusion time performed in critically ill patients.

Our study has several strengths. First, we evaluated a large and detailed database of critically ill patients. This allowed us to select two large groups of patients with distinct clinical settings. The detailed information provided by this database is of utmost importance, because it enables it to expand the baseline characteristics beyond the possibilities of an administrative database. For instance, we were able to match/access the patient data regarding admission serum creatinine, mean MAP, and use of vasoactive drugs in the first 48 hours of ICU stay, sedative mean dose, and its use duration. This judicious matching increases the reliability in the evaluated outcomes.

Our study also has limitations. First, it was performed with a single-center data source. Second, although >8000 patients received propofol in the first 48 hours of ICU stay, we were limited by the relatively low number of patients receiving midazolam. The most important limitation is the retrospective nature of our study. Although we tried to perform a detailed and judicious matching, it is possible that missing baseline characteristics might have influenced the results. Points that need to be carefully considered include the lack of data about the year of admission for each patient as well as the relatively reduced number of patients with sepsis in our cohort. However, we performed a sensitivity analysis for unmeasured confounders and demonstrated that a real association between propofol and

better renal outcomes is highly probable; however, these questions can be clarified only by a randomized clinical trial. The absence of information about nephrotoxic substance administration before ICU admission and other pre-admission data are also important limitations. Moreover, some questions remain regarding whether propofol dose and administration time could be effective in attenuating AKI.

In conclusion, we demonstrated that propofol was associated with fewer adverse renal outcomes, including severe ones such as the need for RRT, in a large cohort of critically ill patients. This reinforces the use of propofol as one of the first-choice sedative agents in mechanically ventilated patients and provides evidence to perform randomized clinical trials using propofol as a promising and clinically available agent, not only in the critically ill patient setting but also in other clinical conditions associated with a high risk of developing AKI.

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Disclosures

None.

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