Original Article

Comparison between midazolam and propofol in acute phase for ventilated patients with sepsis: a *post-hoc* analysis of the DESIRE trial

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Aim: There are few assessments of sedatives during the acute phase under sedation protocols for patients with sepsis. We aimed to compare the influence of different sedation strategies using midazolam and propofol under light sedation on clinical outcomes of ventilated patients with sepsis.

Methods: This study was a post-hoc analysis of data from the dexmedetomidine for sepsis in the ICU Randomized Evaluation (DESIRE) trial. Patients were divided into propofol and midazolam groups based on continuously used drug, and sedation control between groups compared on day three. We assessed the incidence of delirium, length of ICU stay, number of ventilator-free days within the first 28 days, and mortality after 28 days.

Results: The midazolam and propofol groups consisted of 51 and 66 patients, respectively. Both groups had similar characteristics, except for age and emergency surgery. The number of well-controlled sedation patients in the propofol group on day three was significantly higher than that in the midazolam group (odds ratio [OR] 3.9, 95% CI [1.30, 11.7]). The incidence of daily coma and delirium within the initial week was different between groups and increased with midazolam administration (P = 0.0138). The number of Confusion Assessment Method for ICU-positive patients was significantly higher in the midazolam group than in the propofol group (OR 5.71, 95% CI [2.30, 14.2]).

Conclusion: In patients with sepsis required mechanical ventilation, sedation with midazolam based on a light sedation protocol may be associated with inappropriate sedation during the acute phase, with increased coma and delirium as compared to propofol.

Key words: Delirium, midazolam, propofol, sedation, sepsis

INTRODUCTION

IT IS ESTIMATED that approximately 48.9 million people worldwide develop sepsis every year, of which 11 million (22.5%) die. Although there is regional variation, and the mortality rate is decreasing, sepsis remains a serious issue worldwide.[1]

To highlight the importance of respiratory management, about 40–80% of the septic patients in the intensive care unit (ICU) require invasive mechanical ventilation (MV).[2,3] Maintaining light sedation was associated with better clinical outcomes in the management of patients with sepsis who

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[†]See 14 Acknowledgement section for all members of DESIRE Trial Investigators.

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required ventilatory support.[4,5] The clinical guidelines for sedation strategies in intensive care recommend light sedation management from the early phase with an appropriate sedation protocol.[6,7] It was recently reported that controlling light sedation in the acute phase during the initial 48 h-period of intensive care was associated with increased survival, less delirium, and successful ventilator weaning.[8] Therefore, we focused on sedation control during the first 48–72 h of intensive care.

Midazolam and propofol are GABA-A agonists that have traditionally been used as primary sedatives. Midazolam is a convenient drug that has little effect on hemodynamics but has been reported to accumulate within the body, prolonging the period of MV and increasing the risk of delirium in ICU patients.[9–11] Although various studies comparing midazolam and propofol have been conducted, to the best of our knowledge, there are few studies comparing the impact of these drugs on clinical outcomes in patients with sepsis that focus on light sedation during the acute phase.

Therefore, the present study aimed to compare the influence of different sedation strategies using midazolam and propofol under light sedation on clinical outcomes for ventilated patients with sepsis. We utilized data from the dexmedetomidine for sepsis in the ICU Randomized Evaluation (DESIRE) trial.[12]

METHODS

Study design and patients

THIS NESTED COHORT analysis examined data from the DESIRE trial. The DESIRE trial was a multicenter, randomized clinical trial that studied 201 patients with sepsis who required MV and compared sedation strategies between the patients that were and were not administered dexmedetomidine at eight ICUs in Japan from February 2013 until January 2016. This trial was registered with ClinicalTrials.gov (identifier: NCT 01760967) and was approved by the review committees of all relevant agencies. All participants provided informed consent before registration.

In the DESIRE trial, only midazolam, propofol, and dexmedetomidine were used for sedation. Dexmedetomidine was used in a randomized allocation, and the use of midazolam and propofol was at the discretion of the physician in charge. In this sub-analysis, we compared the patients who were administered midazolam without propofol to those who were administered propofol without midazolam as continuous sedation by day 2 after randomization.

Patients who left the ICU by day 2 who did not use either midazolam or propofol, or who were administered both drugs in the initial 2 days of enrollment, were excluded from this analysis. Sedatives administered by bolus, dexmedetomidine, and fentanyl, were not considered for grouping.

Data collection

We collected patients' data on age and sex, emergency operation, day one acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores, C-reactive protein, and procalcitonin levels. Septic shock was defined as having three or more cardiovascular components of the SOFA score and a lactate level of 2 mmol/L or higher on the first day after randomization. In addition, we collected data regarding the duration of stay in the ICU, infection site (abdomen, thorax, or other), 28-day mortality, and ventilator-free days (VFD) during the first 28 days.

The amount of sedation was adjusted and maintained as needed during MV based on the sedation protocol at the discretion of the attending physician. The sedation protocols were also in compliance with the clinical practice guidelines for the sustained use of sedatives and analgesics in critically ill adults.[13]

The targets of sedation depth of the DESIRE trial were a Richmond Agitation-Sedation Scale (RASS) score of 0 (calm) during the day and a RASS score of −2 (lightly sedated) during the night in both groups. According to the previous reports, well-controlled sedation is defined as having a RASS score between −3 and +1 throughout the day spent in the ICU, since ±1 is thought to be an allowable range of clinical and more practical evaluation.[12,14] Delirium was identified based on a positive result from the Confusion Assessment Method for ICU (CAM-ICU) during the initial 7 days,[13] coma was identified based on a RASS score between −4 and −5 throughout 1 day in the ICU.[15] The RASS and CAM-ICU were assessed ≥4×/shift and ≥1×/shift, respectively, as needed by trained nurses in the ICU every day.

The primary endpoint was the achievement of well-controlled sedation (RASS score of −3 to +1) on day 3. Secondary endpoints were the incidence of delirium for the first 7 days, length of ICU stay, number of VFD during the first 28 days, and mortality after 28 days.

We additionally assessed data excluding patients treated with dexmedetomidine and included the results as supplementary data.

Statistical analysis

Categorical variables were expressed as number (%), while continuous variables were expressed as median (interquartile range [IQR]) or mean (standard deviation [SD]). Categorical

variables were compared using the chi-squared test or t-test. Continuous variables were compared using the Wilcoxon rank-sum test.

Multivariate adjusted analysis was performed using logistic regression analysis for well-controlled sedation, CAM-ICU positive, and 28-day mortality rate, while multiple linear regression analysis was used for VFD and length of stay in ICU. We adjusted for age 65 years and older, dexmedetomidine administration, respiratory infections, presence of emergency surgery, and APACHE II score of 23 or higher, as prespecified in the main analysis.

To examine the effect of midazolam and propofol on sedation control and the occurrence of delirium and coma, a generalized linear model (GENMOD procedure with logit function) was used to account for repeated measurements on the same patient. We included the status of patients as the dependent variable and treatment allocation as the independent variable with a repeated variable of each patient. The survival and incidence of delirium over the 7 days treatment period was estimated *via* the Kaplan–Meier method, and differences between groups were evaluated by the log-rank test.

All analyses were performed using the JMP Pro software (version 14; SAS Institute, Cary, NC, USA). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

OF THE 203 patients enrolled in the DESIRE trial, 117 patients were included in this study.

Patient characteristics

Of the 117 patients, 51 and 66 patients were in the midazolam and propofol groups, respectively (Fig. 1). The characteristics of the two groups are shown in Table 1. Of these, 31 (60.8%) in the midazolam group and 39 (59.1%) in the propofol group were men, with a mean age of 67 years (SD, 13.6 years) and 73 years (SD, 12.5 years), respectively. The number of patients with septic shock was 30 (58.8%) in the midazolam and 35 (53%) in the propofol groups. Emergency surgery was more common in the propofol group, with 13 (25.5%) and 30 (45.5%) of patients in the midazolam and propofol groups, respectively, having undergone emergency surgery.

Sedative and opioid usage and dosing in the first week for the midazolam and propofol groups are shown in Table S1.

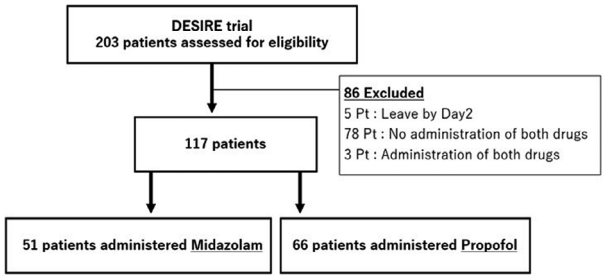

Fig. 1. Flowchart of the patients included in the study. DESIRE, Dexmedetomidine for Sepsis in the Intensive care unit (ICU) Randomized Evaluation.

Table 1. Patient characteristics

	Midazolam group (*n* = 51)	Propofol group (*n* = 66)	*P*-value
Age, years, mean (SD)	67 (13.6)	73 (12.5)	0.014
Sex, male, No. (%)	31 (60.8)	39 (59.1)	0.853
APACHE II score, median (IQR)	23.0 (17–30)	21.5 (16–26)	0.231
SOFA scores, median (IQR)	9 (6–11)	8 (6–11)	0.937
Emergency surgery, No. (%)	13 (25.5)	30 (45.5)	0.026
Shock, No. (%)†	30 (58.8)	35 (53.0)	0.531
C-reactive protein, median (IQR), mg/dL	14.4 (4.6–27.9)	16.5 (5.5–24.4)	0.729
Procalcitonin, median (IQR), ng/mL	6.2 (0.77–30.5)	18.2 (2.7–70.7)	0.724
With dexmedetomidine infusion, No. (%)	14 (27.5)	27 (40.9)	0.130
Site of infections, No. (%)			
Abdomen	14 (27.5)	29 (43.9)	0.067
Lung	23 (45.1)	19 (28.8)	0.068
Others	14 (27.5)	18 (27.3)	0.983

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.
†Shock: Cardiovascular components of the SOFA score ≥ 3 and Lactate ≥2 mmol/L.

Outcomes

For the primary endpoint, the number of patients who were well controlled with sedation on day 3 was 7 (14.9%) in the midazolam group and 19 (33.9%) in the propofol group (odds ratio [OR] 3.91, 95% CI [1.30, 11.7]; Tables 2 and 3).

Table 2. Raw data of main outcomes

	Midazolam group (n = 51)	Propofol group (n = 66)	P-value
Well-controlled sedation on day 3, No. (%)	7/47 (14.9)	19/56 (33.9)	0.026
VFD, mean (SD)	14.9 (10.6)	16.2 (10.5)	0.494
ICU-LOS, mean (SD)	9.1 (1.3)	9.1 (1.2)	0.980
CAM-ICU positive, No. (%)	33 (64.7)	19 (28.8)	0.0001
28 days mortality rate, No. (%)	14 (27.5)	15 (22.7)	0.557

Abbreviations: CAM-ICU, Confusion Assessment Method for the intensive care unit; ICU LOS, Intensive care unit length of stay; VFD, Ventilator-free days.

Table 3. Logistic regression analysis of well-controlled sedation at 48–72 h (day 3) of admission with propofol compared to midazolam

Variable	OR	95% CI	P-value
Well-controlled sedation			
Unadjusted	2.93	[1.10, 7.78]	0.026
Multivariable adjusted	3.91	[1.30, 11.7]	0.015

Abbreviations: OR, odds ratio: The odds of the propofol group against the midazolam group.

For the secondary endpoint, there was a significant difference in the number of CAM-ICU-positive patients: 33 (64.7%) in the midazolam group and 19 (28.8%) in the propofol group (OR 5.71, 95% CI [2.30, 14.2]; Tables 2 and 5). Although no significant difference was observed between groups regarding daily sedation control analysis as repeated measurements for the initial week (range, midazolam 5.9–33.3% versus propofol 4.5–40%; P = 0.78) (Fig. 2A), the incidence of daily coma and delirium within the first week was suggested to increase with the use of midazolam (range, midazolam 29.4–53.8% versus propofol 39.3–65.2%; P = 0.0138; Fig. 2B, Figure S1).

The VFD, ICU stay, and 28-day mortality were not different between groups (Tables 2, 4 and 5).

DISCUSSION

THE RESULTS OF this study suggested that the administration of midazolam was associated with deeper sedation and a higher risk of coma and delirium during the acute phase compared to propofol, even under light sedation protocols, in ventilated patients with sepsis.

Maintaining light sedation in ICU patients is associated with improved clinical outcomes, namely, increased survival and less delirium.[8] Previous studies reported that midazolam prolonged the time to light sedation compared to propofol.[16,17] In our study, midazolam also resulted in significantly deeper and more inappropriate sedation than propofol in the acute phase (day 3 of hospitalization) despite practicing light sedation protocols. A cohort study in a multicenter ICU reported that maintaining light sedation in the first 48 h is important.[8] Based on the previous findings, we focused on sedation management on day 3 after hospital arrival.

Previous reports show a high frequency of delirium in 60–80% of patients in the ICU; therefore, preventing delirium is a common and an issue of high concern.[18] Delirium can be caused by multiple factors including sepsis-related encephalopathy, and is associated with an increase in mortality, prolonged ICU stay, and deterioration of cognitive function after discharge from the ICU.[19,20] In a prospective cohort study of 650 patients in a multicenter ICU, unstable sedation control using RASS was associated with the occurrence of delirium.[21] To date, no randomized clinical trials have clarified the risk of delirium incidence by comparing midazolam and propofol.[10,11] In this study, use of midazolam may be associated with increased delirium, even with a light sedation protocol.

Many previous comparative studies of midazolam and propofol have reported prolonged duration of ventilator weaning, but there was no significant difference in ICU length of stay or mortality between the groups.[9–11,22] In our study, similar to previous studies, there was no difference in ICU length of stay, 28-day VFD, or mortality suggesting that midazolam was not suitable for achieving well-controlled sedation and preventing delirium and coma.

This study has some limitations. This is a *post-hoc* analysis and the sample size was limited. The administration of midazolam and propofol was left to the discretion of the physician in charge. Our definition of well-controlled sedation and the assessment period might not be comparable to those in other studies, although our definition was based on the applicable guidelines and considered to be clinically relevant.[13] Delirium is also difficult to accurately assess in

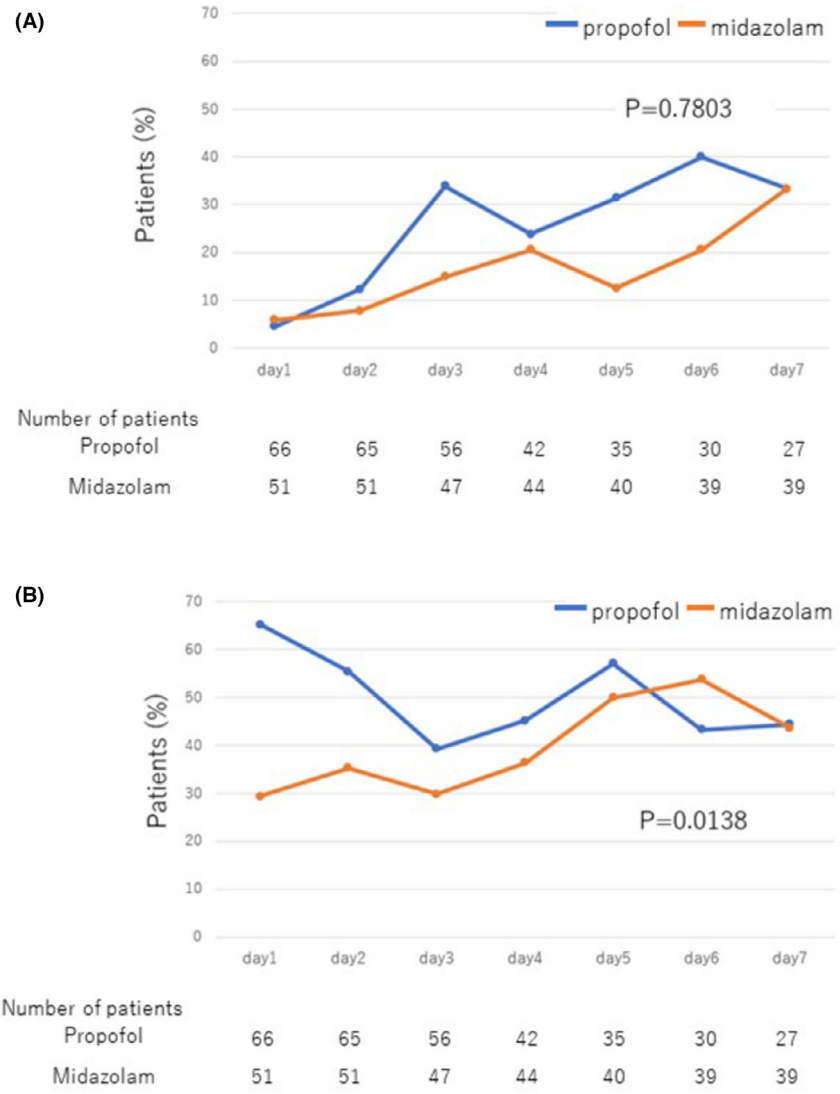

Fig. 2. (A) Ventilated patients with well-controlled sedation for 7 days in the midazolam and propofol arms (GENMOD procedure for repeated measures). (B) Ventilated patients free from delirium and coma for 7 days in the midazolam and propofol arms (GENMOD procedure for repeated measures).

patients with sepsis as its cause is multi-factorial. Although there were significant differences in age and incidence of emergency surgery in the patient demographics, both were included in the predetermined adjustments used in the main analysis.[12,23] The midazolam and propofol groups included patients treated with and without dexmedetomidine as a given allocation in the original study design. However, in a complementary analysis that remove the effect of dexmedetomidine, the results were also the same (Fig. S2, Table S2).

In conclusion, in septic patients requiring mechanical ventilation, even with protocols for light sedation management, the use of midazolam may be associated with more inappropriate sedation and increased delirium as compared to propofol. Further prospective studies are required to validate this finding.

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Table 4. Multiple linear regression analysis of VFD and ICU length of stay with midazolam compared to propofol

	Mean difference	95% CI	*P*-value
VFD			
Unadjusted	−1.35	[−5.24, 2.54]	0.494
Multivariable adjusted	−0.25	[−4.32, 3.81]	0.901
ICU LOS			
Unadjusted	−0.04	[−3.58, 3.49]	0.980
Multivariable adjusted	−0.46	[−4.12, 3.19]	0.800

Abbreviations: ICU LOS, intensive care unit length of stay; VFD, Ventilator-free days.

Table 5. Logistic regression analysis of CAM-ICU positive and 28 days mortality rate with midazolam compared to propofol

Variable	OR	95% CI	P-value
CAM-ICU positive			
Unadjusted	4.54	[2.07, 9.92]	0.0001
Multivariable adjusted	5.71	[2.30, 14.2]	0.0002
28 days mortality rate			
Unadjusted	1.28	[0.55, 2.98]	0.557
Multivariable adjusted	1.00	[0.37, 2.64]	0.990

Abbreviations: CAM-ICU, Confusion assessment method for the intensive care unit; OR, odds ratio.
The odds of the midazolam group against the propofol group.

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DISCLOSURE

Approval of the research protocol with approval number and Committee name: This study is a *post hoc* subgroup analysis of the DESIRE trial, which was a randomized controlled trial that included eight Japanese intensive care units. The original study was approved by the review boards of all relevant institutions.
Informed consent: All participants provided written informed consent prior to enrolment.
Registry and registration no. of the study/trial: Clinicaltrials.gov: NCT01760967; January 1, 2013.
Animal studies: N/A.
Conflict of interest: None.

DATA AVAILABILITY STATEMENT

THE DATASETS GENERATED and analyzed during the current study are not publicly available because of privacy concerns and institutional policy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Kaplan–Meier curves of developing delirium in the first 7 days in the midazolam and propofol groups.

Figure S2 Flowchart of the study patients who were not treated with dexmedetomidine

Table S1 Sedative and opioid usage and dosing in the first week.

Table S2 Characteristics and analysis of study patients who were not treated with dexmedetomidine.