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Original Article

Prolonged Double-Low Time and the Incidence of Postoperative Delirium in Surgical ICU Patients

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An intraoperative double-low condition is defined as concurrent low values for bispectral index (BIS) and mean arterial pressure (MAP), and may predict perioperative outcomes. We hypothesized that prolonged double-low times might be associated with an increased incidence of postoperative delirium. We conducted a single-center retrospective observational study on patients who had been admitted to our hospital's intensive care unit (ICU) after surgery and whose BIS and MAP data had been recorded during general anesthesia. The primary outcome was the incidence of postoperative delirium. A double-low condition was defined as BIS <45 and MAP <75 mmHg. The total double-low time was calculated in 1-min increments and used to divide the patients into quintiles. Multiple logistic regression analyses were conducted. Among the 334 patients included in the study, the incidence of postoperative delirium was 15.6% (n=52). Multiple logistic regression analysis revealed that a prolonged double-low time, defined as a total double-low time of >42 min (*i.e.*, third, fourth, and fifth quintiles), was significantly associated with an increased incidence of postoperative delirium (adjusted odds ratio: 2.61, 95% confidence interval: 1.27-5.37, $p=0.009$). Prolonged double-low time during general anesthesia was independently associated with an increased incidence of postoperative delirium in surgical ICU patients.

Key words: postoperative delirium, bispectral index, hypotension, double-low condition, general anesthesia

Postoperative delirium is a serious condition occurring in 5.1-52.2% of patients after noncardiac surgery, although the incidence varies according to the type of surgery [1]. Postoperative delirium is associated with prolonged hospital stays and an increased risk of mortality [2,3]. Potential risk factors for postoperative delirium include predisposing factors such as older age, dementia, and alcohol use, as well as precipitating factors such as benzodiazepine administration, abnormal electrolytes, and pain [4]. However, there are only a limited number of modifiable risk factors in the perioperative setting, and there is no effective strategy for the prevention of postoperative delirium among the general patient population.

A double-low condition is defined as concurrent low bispectral index (BIS) and mean arterial pressure (MAP) values [5,6]. Prolonged double-low time may be associated with infectious, renal, and neurological complications, as well as prolonged hospitalization and increased mortality [5,6]. Several reports suggest that either a low BIS value [7,8] or hypotension [9] is associated with a higher incidence of postoperative delirium; however, it is unclear whether a double-low con-

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dition is associated with the incidence of postoperative delirium. Therefore, this retrospective study aimed to evaluate the intraoperative BIS and MAP data (total: 96,383 min in 1-min intervals) to determine whether a prolonged double-low time was associated with an increased incidence of postoperative delirium.

Materials and Methods

Study design, setting, and patients. This retrospective study evaluated patients who had undergone elective or emergency surgery under general anesthesia followed by admission to the intensive care unit (ICU) at the Okayama University Hospital between January and December 2015. The retrospective study protocol was approved by the institutional review board on November 17, 2017 (K1712-033). Patients who had undergone BIS and MAP monitoring while under anesthesia were eligible. Patients were excluded if they were < 18 years of age, if they were undergoing obstetric surgery or intravascular cardiology procedures, if the duration of anesthesia was < 3 h, or if they had incomplete or missing data *(i.e.*, missing data on BIS or MAP over 10 consecutive time points, or MAP values of ≥ 150 mmHg or ≤ 10 mmHg over 10 consecutive time points).

Anesthetic management. Anesthesia was induced using propofol (1-2 mg/kg), rocuronium (0.6 mg/kg), and/or remifentanil (0.3 μg/kg/min). All patients underwent tracheal intubation and mechanical ventilation. The anesthetic management was determined by the attending anesthesiologist, which generally involved maintenance using total intravenous anesthesia (2.5-3.5 μg/mL propofol at the effect site using a target-controlled infusion system) or volatile anesthetics (sevoflurane at 1-1.5% or desflurane at 4-5%). The maintenance was also combined with remifentanil (0.05-0.3 μg/kg/min), fentanyl (2-5 μg/kg), epidural anesthesia, or a peripheral nerve block.

Definitions. The definition of a double-low condition was the concurrent presence of a BIS value of < 45 and an MAP of < 75 mmHg, based on a previous study [5]. The BIS sensor (Covidien, Mansfield, MA, USA) was placed on the patient's forehead according to the recommended procedure and then connected to the BIS monitor. The BIS value is a continuous processed electroencephalogram (EEG) parameter that correlates to the patient's level of hypnosis, where 100 = awake and 0 = flat-line EEG, with values of 40-60 regarded as within the appropriate range under general anesthesia. A radial arterial line was used to monitor MAP in all patients. Admission to the ICU depended on the type of surgery (*e.g.*, major surgery including cardiovascular, abdominal, thoracic, and neurosurgery), emergency surgery, and the determination by the attending anesthesiologist concerning the severity of the patient's condition. The presence of postoperative delirium was monitored by the ICU nurses 3 times per day (morning, afternoon, and at night) using the Confusion Assessment Method for the ICU [10, 11]. In addition, the ICU nurses screened the patients whenever they exhibited potential signs of postoperative delirium. Postoperative delirium was defined as a positive result according to the Confusion Assessment Method for the ICU at any time during the patient's ICU stay.

Data extraction. Intraoperative BIS and MAP data were extracted from electronic anesthesia records, where they had been recorded at 1-min intervals. These data were assessed to identify the number of double-low conditions during a period from 1 h after anesthesia induction to 1 h before the end of anesthesia. Data were also retrospectively collected regarding potential confounding factors: age, blood loss, duration of anesthesia, emergency surgery status, and the American Society of Anesthesiologists (ASA) physical status. The patients' electronic medical records for their ICU stay were reviewed to retrospectively identify postoperative delirium.

Statistical analyses. Categorical variables were compared using Fisher's exact test. Non-normally distributed continuous variables were compared using the Mann–Whitney *U* test. The total double-low time was calculated for each patient, and the patients were divided into quintiles to evaluate the relationship between double-low time and postoperative delirium. We defined the first through fifth quintiles as groups 1 through 5, respectively. Prolonged double-low time was defined as the latter three groups (groups 3, 4, and 5). The association between prolonged double-low time and postoperative delirium was evaluated using a multiple logistic regression model adjusted for *a priori* selected potential confounding factors, including age, ASA physical status, and emergency surgery status. Age was assessed as a continuous variable in the model. ASA physical status and emergency surgery were also assessed as dichotomous variables. We selected these variables as well-known and important risk factors for postoperative delirium. Collinearity was assessed by calculating the variance inflation factor. Subgroup analyses were performed according to the age and ASA physical status. Differences were considered statistically significant at two-sided p-values of < 0.05. The statistical analyses were performed using EZR (version 1.40; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) [12].

Results

Patients. During the study period, 523 patients were assessed for eligibility (Fig. 1). Sixteen patients were excluded because they were < 18 years old, and 150 patients were excluded because of insufficient data. In addition, 2 patients were excluded because of ineligible surgery types, and 21 patients were excluded based on their short duration of anesthesia. Thus, the study ultimately included 334 patients.

Patient characteristics. The patients' characteristics are presented in Table 1. The overall incidence of postoperative delirium was 15.6% (52 patients). A comparison of the groups with and without postoperative delirium revealed no significant differences in terms of sex, body mass index, blood loss during surgery, or duration of anesthesia. Patients with postoperative delirium were older (median: 73 years [interquartile range: 64-81 years] vs. 66 years [interquartile range: 55-73 years], $p < 0.001$) and more likely to have undergone emergency surgery (9.6% vs. 2.8%, $p = 0.04$) than those without. Moreover, patients with postoperative delirium were more likely to have an ASA physical status of 3-4 (65.4% vs. 35.1%, $p < 0.001$) and to receive volatile anesthetics (44.2% vs. 29.1%, $p = 0.04$), and were less likely to receive epidural anesthesia or peripheral nerve block (25.0% vs. 51.1%, $p < 0.001$) than those without. Moreover, patients with postoperative delirium had a significantly longer total double-low time (median: 84 min [interquartile range: 44-151 min] vs. 56 min [interquartile range: 22-133 min], $p = 0.04$) than those without.

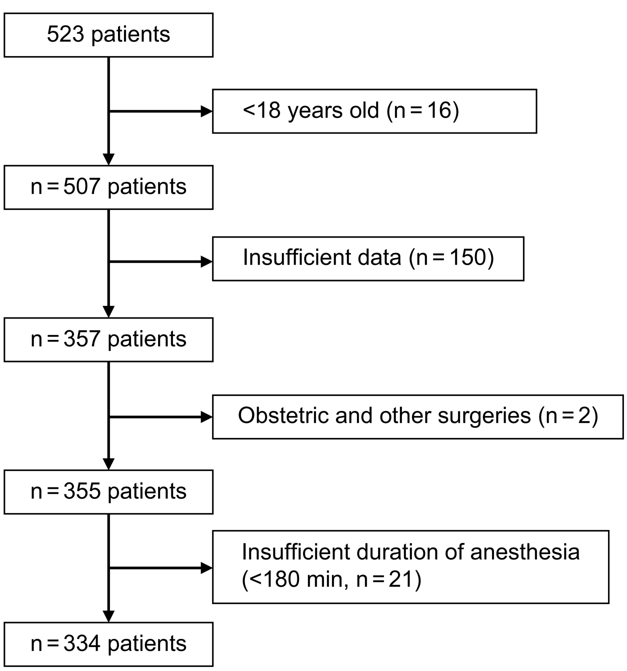

Fig. 1 Study flowchart.

Double-low time and postoperative delirium. The patients were assigned to quintiles according to their total double-low time (group 1: 0-15 min; group 2: 16-42 min; group 3: 43-87 min; group 4: 88-159 min; group 5: 160-503 min). The incidences of postoperative delirium were 9.1% in group 1, 10.4% in group 2, 20.6% in group 3, 19.4% in group 4, and 18.2% in group 5 (Fig. 2). Because a clear upward trend of the incidence of postoperative delirium was observed between groups 1-2 (a total double-low time of ≤ 42 min) and groups 3-5 (a total double-low time of > 42 min), we defined groups 3-5 as having prolonged double-low time. Multivariable logistic regression analysis showed that prolonged double-low time was independently associated with postoperative delirium (adjusted odds ratio: 2.61, 95% confidence interval [CI]: 1.27-5.37; $p = 0.009$) (Table 2).

Subgroup analyses. We evaluated the association between prolonged double-low time and postoperative delirium in various dichotomized subgroups (age [< 65 years vs. ≥ 65 years] and ASA physical status [1-2 vs. 3-4]). Among patients who were ≥ 65 years old, a prolonged double-low time was significantly associated with postoperative delirium (adjusted odds ratio: 2.38, 95% CI: 1.06-5.34; $p = 0.035$) (Fig. 3). A prolonged double-low time was also significantly associated with postoperative delirium among patients with an ASA physical status of 1-2 (adjusted odds ratio: 4.16, 95% CI: 1.14-15.30; $p = 0.031$).

Table 1 Baseline patient characteristics

	All patients (n = 334)	Postoperative delirium (n = 52)	No postoperative delirium (n = 282)	*P*-value
Age (years)	67 (56–74)	73 (64–81)	66 (55–73)	< 0.001
Female sex	157 (47.0)	29 (55.8)	128 (45.4)	0.18
Body mass index (kg/m^2)	22.3 (19.8–24.6)	22.2 (20.1–25.5)	22.4 (19.8–24.6)	0.59
ASA PS, n (%)				
1–2	201 (60.2)	18 (34.6)	183 (64.9)	< 0.001
3–4	133 (39.8)	34 (65.4)	99 (35.1)	
Emergency surgery, n (%)	13 (3.9)	5 (9.6)	8 (2.8)	0.04
Anesthesia, n (%)				
Volatile anesthetics	105 (31.4)	23 (44.2)	82 (29.1)	0.04
Total intravenous anesthesia	229 (68.6)	29 (55.8)	200 (70.9)	
Epidural anesthesia or peripheral nerve block	157 (47.0)	13 (25.0)	144 (51.1)	< 0.001
Blood loss during surgery (mL)	130 (32–450)	190 (28–945)	125 (42–374)	0.13
Duration of anesthesia (min)	316 (230–446)	374 (201–547)	302 (230–432)	0.24
Total double-low time (min)	58 (25–135)	84 (44–151)	56 (22–133)	0.04
Type of surgery				
General surgery	106 (31.7)	8 (15.4)	98 (34.8)	–
Thoracic surgery	94 (28.1)	10 (19.2)	84 (29.8)	
Orthopedics	41 (12.3)	5 (9.6)	36 (12.8)	
Cardiovascular surgery	26 (7.8)	8 (15.4)	18 (6.4)	
Neurosurgery	26 (7.8)	7 (13.5)	19 (6.7)	
Otorhinolaryngological surgery	21 (6.3)	8 (15.4)	13 (4.6)	
Other	20 (6.0)	6 (11.5)	14 (5.0)	

Data are presented as numbers (%) or medians (interquartile ranges).
ASA PS, American Society of Anesthesiologists physical status.

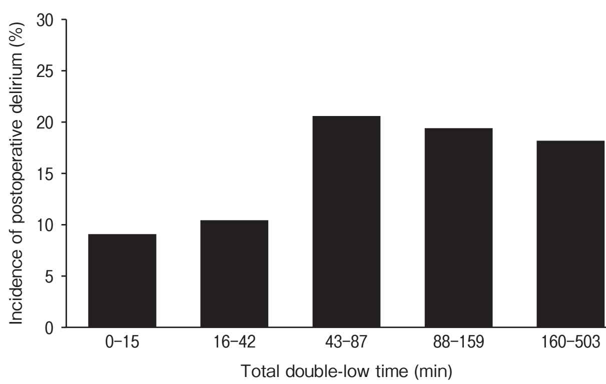

Fig. 2 Incidences of postoperative delirium according to total double-low time quintile. The incidences of postoperative delirium were 9.1% in the first quintile (total double-low time: 0–15 min), 10.4% in the second quintile (16–42 min), 20.6% in the third quintile (43–87 min), 19.4% in the fourth quintile (88–159 min), and 18.2% in the fifth quintile (160–503 min).

Table 2 Multiple logistic regression analysis of the risk factors for postoperative delirium

	Adjusted odds ratio (95% CI)	*P*-value
Age (years)	1.03 (1.01–1.06)	0.016
ASA PS 3–4	2.81 (1.47–5.39)	0.002
Emergency surgery	4.76 (1.24–18.30)	0.023
Prolonged double-low time*	2.61 (1.27–5.37)	0.009

*Total double-low time of > 42 min
ASA PS, American Society of Anesthesiologists physical status; CI, confidence interval. The maximum variance inflation factor was 1.05.

Discussion

Summary. This single-center retrospective study evaluated whether a prolonged double-low time is associated with an increased incidence of postoperative delirium. The study included 334 patients who had undergone surgery under general anesthesia and had been admitted to our ICU. The incidence of postoperative delirium in our patient group was 15.6% (52 patients), and prolonged double-low time was independently associated with the incidence of postoperative delirium. Subgroup analyses suggest that a prolonged double-low time might be associated with an

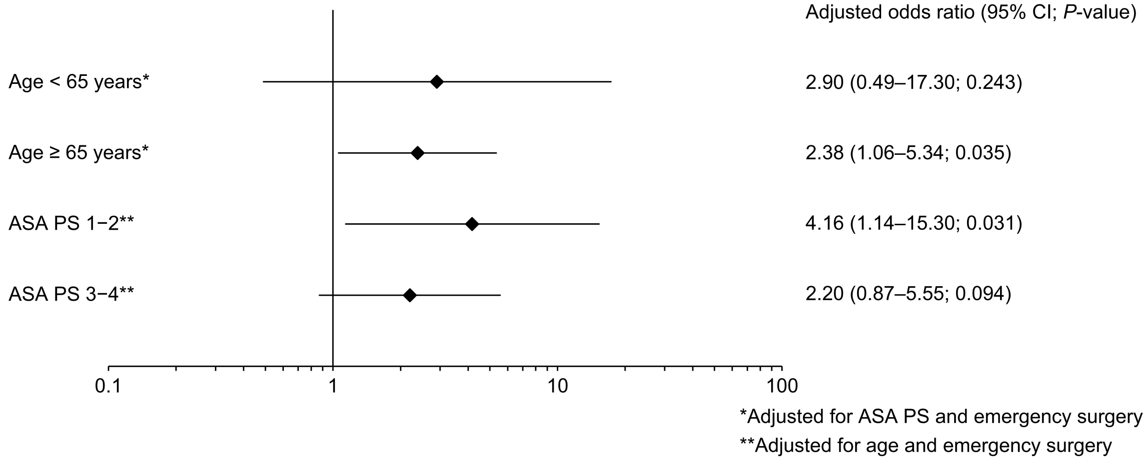

Fig. 3 The associations between postoperative delirium and prolonged double-low time (>42 min) among different subgroups. ASA PS, American Society of Anesthesiologists physical status; CI, confidence interval.

increased incidence of postoperative delirium among older patients (aged ≥65 years) and low-risk patients (ASA physical status 1 or 2).

Main findings. The incidence of postoperative delirium found in this study (15.6%) is similar to the 21.5% incidence reported in an earlier systematic review and meta-analysis, which evaluated patients who had undergone noncardiac surgery [13]. However, we included only patients who were admitted to the ICU after surgery. At our center, ICU nurses routinely evaluate their patients for postoperative delirium (3 times per day) using the Confusion Assessment Method for the ICU, which is a valid screening tool. In addition, the nurses generally screen patients if they exhibit potential signs of postoperative delirium. Thus, an incidence of 15-20% for postoperative delirium in the surgical ICU appears to be a reliable estimate based on the current guidelines [14, 15].

We found that a prolonged double-low time was significantly associated with an increased incidence of postoperative delirium. A previous retrospective study indicated that a prolonged double-low time is associated with mortality and morbidity after cardiac surgery [6], and in a prospective trial of patients who underwent noncardiac surgery, a total double-low time of >60 min was associated with an approximately two-fold increased risk of mortality [5]. Thus, patients with a prolonged double-low time may be in a relatively critical condition. Our results suggest that the incidence of postoperative delirium does not increase proportionally with the total double-low time but that it is generally higher for times >42 min, which might be a clinically relevant cutoff value. Given that there are few modifiable risk factors for postoperative delirium, the likelihood of postoperative delirium might be reduced by developing strategies to minimize double-low time (*e.g.*, concomitant goal-directed hemodynamic therapy and BIS-guided anesthesia; that is, practical fluid therapy and vasopressor administration combined with regulation of anesthetics via BIS monitoring).

We also observed that patients with postoperative delirium were older, had a higher ASA physical status, and were more likely to have undergone emergency surgery than those without. These are considered risk factors for postoperative delirium based on the current guidelines and a recent statement from the American Geriatrics Society [14, 15]. For example, patients who are ≥65 years old [14, 15] and patients with an ASA physical status of >2 [16-18] both have a risk of developing postoperative delirium. We observed that ≥65-year-old patients had a slightly increased incidence of postoperative delirium (19.9% vs. 15.6%), and the incidence increased to 32.4% among patients ≥75 years old. Moreover, incidences of postoperative delirium were 11.0% among patients with an ASA physical status of 2, 21.8% among patients with an ASA physical status of 3, and 35.3% among patients with an ASA physical status of 4, indicating that the incidence of postoperative delirium increases with ASA physical status.

The subgroup analysis suggested that older patients and low-risk patients might be vulnerable to a risk of prolonged double-low time and thereby an increased risk of postoperative delirium. It is assumed that surgical patients are mainly low-risk patients [19]. In addition, because societies worldwide are facing increases in their aged populations, the number of older patients undergoing surgery is expected to increase. Thus, these subgroups would eventually be expected to constitute the majority of the surgical population. It might therefore be of critical importance to perform further research focused on these patients. On the other hand, high-risk patients were not found to be at risk of prolonged double-low time. There is, however, a need to consider the results of analysis of restricted small sample size and confounding factors.

Limitations. This study has some limitations. First, it is a single-center retrospective study restricted to patients admitted to a surgical ICU after surgery. Moreover, the design and missing data for some patients prevented us from conducting a more comprehensive analysis of risk factors for postoperative delirium with adjustment for considerable potential confounding factors. Thus, the generalizability of our findings is limited. However, we note that our hospital and ICU have all the typical characteristics of a tertiary ICU in a developed country, suggesting a degree of external validity. Thus, the restriction of the patients admitted to the ICU may have allowed us to reduce some effects of potential confounding factors. This notion is supported by the similarity between the incidence of postoperative delirium in our study to those reported in previous studies [13]. The second limitation is that we defined the total double-low time of >42 min as a prolonged double-low time in this study. However, it is unclear whether the definition is a clinically relevant cutoff value. Thus, further study is required to confirm a cutoff value for prolonged double-low time. Third, we did not confirm the reliability of the evaluation of postoperative delirium by ICU nurses in this study. However, our ICU routinely assesses the Confusion Assessment Method for the ICU, regardless of the requirements of this study. Thus, we think that ICU nurses performed sufficient evaluation of postoperative delirium in the current study. Fourth, we performed multiple logistic regression with an excess of independent variables despite the small sample size in subgroup analysis. However, we thought it was clinically meaningful to explore the possibility of the effect of double-low condition in specific subgroups of patients to develop potential hypotheses for further study. Fifth, because this study focused on the double-low condition, we analyzed only the association with double-low time and did not consider how associations between postoperative delirium and only low BIS values or only hypotension might compare to our findings.

In conclusion, we found that a prolonged double-low time during general anesthesia was independently associated with the incidence of postoperative delirium in surgical ICU patients. Moreover, subgroup analyses suggest a significant association between a prolonged double-low time during general anesthesia and postoperative delirium in older patients (aged ≥ 65 years) and low-risk patients. Our findings highlight the need for future prospective interventional studies, especially in these subgroups of patients.

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