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Influence of intraoperative low bispectral index value on postoperative mortality and delirium

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서울대학교 대학원
의학과 마취통증의학전공
윤 수 혁

ABSTRACT

Influence of intraoperative low bispectral index value on postoperative mortality and delirium

Soohyuk Yoon
Department of Anesthesiology and Pain Medicine
College of Medicine
The Graduate School
Seoul National University

Background: The relationship between intraoperative low bispectral index (BIS) values and poor clinical outcomes has been controversial. The purpose of this study was to investigate the influence of intraoperative low BIS values on postoperative mortality and delirium in patients undergoing major abdominal surgery.

Methods: This retrospective study analyzed 1,862 cases of general anesthesia. We collected the cumulative time of BIS values below 20 and 40 as well as electroencephalographic (EEG) suppression, and we documented the incidences in which these states were maintained for at least 5 minutes. Durations of intraoperative mean arterial pressures (MAP) less than 50 mmHg were also recorded. Multivariable logistic regression was

used to evaluate the association between suspected risk factors and postoperative outcomes (postoperative mortality and delirium).
Results: Ninety-day mortality, 180-day mortality and incidence of delirium were 1.5%, 3.2% and 1.6% respectively. The cumulative time for BIS values falling below 40 coupled with MAP falling below 50 mmHg was associated with 90-day mortality [odds ratio (OR) = 1.260, P = 0.019]. We found no association between BIS values and 180-day mortality. With respect to predictors of postoperative delirium, cumulative time of EEG suppression (OR = 1.045, P < 0.000) and cumulative time of intraoperative MAP below 50 mmHg (OR = 1.201, P = 0.001) were both associated with postoperative delirium.
Conclusion: Delicate adjustment of anesthetic depth is important to avoid excessive brain suppression, which could be associated with postoperative mortality and delirium.

Keywords: bispectral index, intraoperative hypotension, postoperative mortality, delirium
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INTRODUCTION

Monitoring anesthesia depth is essential for providing optimal anesthesia management as it enables the maintenance of adequate anesthesia level (1). The bispectral index (BIS) monitor is the most commonly used device for monitoring depth of anesthesia using electroencephalography (EEG). The BIS was initially introduced to prevent intraoperative awareness and a BIS value between 40 and 60 was considered to correspond with an adequate depth of anesthesia. BIS usage can reduce the risk of intraoperative awareness as well as facilitate faster recovery after general anesthesia by enabling the anesthesiologists to appropriately adjust the anesthetic dose (2, 3). Recently, there has been a growing interest in how the depth of anesthesia monitored using BIS affects postoperative outcomes.

Several studies have suggested an association between low BIS value (< 40 or 45) and postoperative mortality (4–6). However, data on a definite relationship between these remain inconclusive (7, 8). Daniel and colleagues proposed that the low mean arterial pressure (MAP) during low minimum alveolar concentration (MAC) of inhalation anesthetics, especially when combined with low BIS value (< 46), was a predictor of mortality (9). Whereas, Kertai's study found no evidence that either BIS monitoring or avoidance of prolonged periods of low BIS values (i.e., below 45) decreased intermediate-term mortality (7). One study, however, showed that EEG burst suppression recorded by BIS monitoring increased mortality in critically ill sedated patients (10). Another study showed an association between intraoperative EEG suppression and postoperative mortality, but only when EEG suppression was concomitant with low MAP (11).

Intraoperative BIS monitoring can reduce unnecessary anesthetic exposure and lower the incidence of postoperative delirium and cognitive dysfunction (12). Similar studies have found that the percentage of episodes of deep anesthesia (BIS value < 20) and intraoperative EEG suppression could independently predict postoperative delirium (13, 14). Bruhn and colleagues revealed that BIS is inversely associated with suppression ratio when the suppression ratio is greater than 40 or 50 (15, 16). Therefore, extremely low BIS value (< 20) may correspond to the high suppression ratios during anesthesia, which could be a sign of unnecessarily deep anesthesia (17) and lead to poor neurologic outcomes (18).

Intraoperative low BIS values and hypotension can have an effect on postoperative mortality and delirium. However, it remains unclear whether low BIS values can affect postoperative outcomes when such low values are concomitant with hypotension. The relationship between the duration of low BIS value and poor clinical outcomes also remains to be determined. The primary goal of this study was to determine whether intraoperative EEG suppression, low BIS value (< 40) and extremely low BIS value (< 20) are associated with postoperative mortality and delirium in patients who underwent major abdominal surgery.

METHODS

This study received approval from the Institutional Review Board of Seoul National University Hospital (H-1801-031-913).

Patient Population

The intraoperative data used in this study were obtained from the registry of the "Registry Construction of Intraoperative Vital Signs and Clinical Information in Surgical Patients" study (H-1408-101-605, NCT02914444), which was designed to store intraoperative time-synchronized data from multiple anesthesia devices including patient monitors, anesthesia machines, BIS monitors, cardiac output monitors, and target-controlled infusion pumps by use of the 'Vital Recorder' (VitalDB team, Seoul, Korea) program. Using this registry, we could obtain complete intraoperative data (BIS-derived values, MAPs, and anesthetic concentrations).

Data collected for this study came from adult patients who underwent surgeries between August 2016 and June 2017 under general anesthesia with BIS monitoring (BIS Vista, Covidien, Dublin, Ireland). The surgical procedures performed included abdominal surgeries on the gastrointestinal tract, liver, biliary tract, and pancreas.

Data from the following cases were excluded: patients under 18 years old, patients with a history of dementia or delirium, cases with a more than 10% loss of BIS data, cases with missing BIS and MAP data more than 60 seconds, anesthesia times of less than 60 minutes, incomplete data on mortality, and reoperations during the period of analysis.

Data Collection

Vital sign data and clinical information pertaining to the cases were retrospectively analyzed. The data included patient's diagnosis, age, sex, height, weight, type of operation, duration of anesthesia, type of anesthesia used, propofol concentration, minimum alveolar concentration (MAC) of volatile anesthetics, intraoperative BIS values, and arterial blood pressure. When MAP was less than 20 mmHg or greater than 200 mmHg, and when BIS was 0, these values were regarded as missing values.

To investigate the relationship between the duration of low BIS value maintenance and postoperative outcomes, we estimated the cumulative time in which BIS values were less than 20 or 40 and designated these as "bis20_dur" and "bis40_dur" respectively. To calculate total time of EEG suppression, designated as "eegsup_dur", we used a suppression ratio. The suppression ratio is the percentage of time over the last 63-second period in which the signal is considered to be in the suppressed state. As an example, a suppression ratio of 40 would mean "isoelectric over 40% of the last 63 seconds". After documenting suppression ratios at every second during anesthesia, we estimated the total time during which a patient's EEG was suppressed by summing each case's fractional suppression ratios applying a method used previously (11). Lastly, we divided the sum by 60 to convert seconds to minutes and then by 100 to make percentages absolute numbers. To investigate the effects of short duration of brain suppression on clinical outcomes, we looked at the incidence in which cumulative time of BIS values less than 20 or 40 and EEG suppression lasted more than 5 minutes (bis20_5min, bis40_5min, and eegsup_5min respectively). To evaluate the influence of hypotension, we estimated the total time that MAP was lower than 50 mmHg (map50_dur) considering previous study (19). We also calculated the cumulative time that MAP was less than 50 mmHg and BIS values were less than 20 or 40 simultaneously (bis20map50_dur or bis40map50_dur).

Potential clinical risk factors of postoperative mortality and delirium were determined by clinical relevance or significance following a previous study (11). We reviewed electronic medical records to retrieve the variables related to postoperative mortality and delirium. They included American Society of Anesthesiologists (ASA) physical status, past medical histories including the presence of aortic stenosis, congestive heart failure, coronary artery disease, hypertension, peripheral vascular occlusive disease, dysrhythmia, chronic obstructive pulmonary disease, stroke, malignancy, diabetes mellitus, sleep apnea, social history of smoking and drinking, and preoperative laboratory test results including hemoglobin (g/dL) and albumin (g/dL). Medication history of anticonvulsants, benzodiazepine and opiates were also reviewed.

Postoperative Outcome

Mortality data were obtained from the Korean Ministry of the Interior and Safety using the resident registration number for each patient in February 2018. In this process, every piece of personal information collected was encrypted so as to maintain patient confidentiality. Mortality data were divided into 90-day postoperative mortality and 180-day mortality to compare early-to-intermediate term and intermediate-to-long term outcomes (20).

The incidence of postoperative delirium during hospital stay was estimated by reviewing electronic medical records. The presence of postoperative delirium was defined in two ways: (1) Patients who were diagnosed with postoperative delirium by a neuropsychiatrist and (2) Patients who were prescribed haloperidol by the attending physician in the surgical intensive care unit based on the Confusion Assessment Method.

Statistical Analysis

Normality of continuous variables was verified with Kolmogorov-Smirnov test. Differences between patients with and without postoperative mortality and delirium were evaluated with Student's t-test or Mann-Whitney U test for continuous variable and the Chi-square test or Fisher's exact test for categorical variable as appropriate.

In the univariable analysis, each variable of the data was analyzed by binary logistic regression in 'enter' method as an independent variable of postoperative mortality or delirium. Variables yielding P-values under 0.2 in the univariable analysis were selected as potential risk factors for multivariable analysis.

We used 2-step multivariable analysis to select more reliable variables considering multicolinearity because some BIS or MAP derived variables had close relationship. In the first step, among the selected risk factors from univariable analysis, variable considered to have a multicolinearity was separately included in binary logistic regression with 'enter' method with other potential risk factors not related to BIS or MAP, after excluding possibly related variables. In this step, we removed several BIS or MAP derived variables not yielding *P*-values under 0.05

In second step, selected BIS or MAP derived variables in first step and other potential risk factors not related to BIS or MAP in univariable analysis were included in final multivariable logistic regression analysis in 'backward LR' method. Variables remaining in the final logistic regression model were regarded as significant risk factors.

The Hosmer-Lemeshow goodness-of-fit test was used to compare the estimate with the observed likelihood of outcomes. All statistical analyses were performed using SPSS software version 23 (IBM Corp., Armonk, New York, USA).

RESULTS

The total number of cases during the period in the H−1408−101−605 registry were 6,423 and we included 2,562 cases according to surgical procedure. After applying exclusion criteria, a total of 1,862 records were included. Causes of exclusion are described in a CONSORT flowchart (Figure 1).

In the study cohort, 90−day postoperative mortality, 180−day postoperative mortality and incidence of delirium were 1.5%, 3.2% and 1.6%, respectively. Demographics and basic patient characteristics, specifics of the operation and anesthesia, numeric details of the BIS−derived variables and other covariates are summarized with their mean wtih standard deviation (SD) or number with percentage (%) in Table 1. The mean cumulative times that the BIS values were less than 20 and 40 were 0.5 (SD 4.2, 95% CI 0.3−0.7) and 70.5 minutes (SD 73.2, 95% CI 67.2−73.8) respectively. The mean cumulative time of EEG suppression was 1.6 minutes (SD 6.6, 95% CI 1.3−1.9). Furthermore, the mean cumulative times that MAP was less than 50 mmHg while the BIS values were less than 20 and 40 were 0.01 (SD 0.11, 95% CI 0.00−0.01) and 0.34 (SD 0.92, 95% CI 0.29−0.38) minutes, respectively.

The number of patients whose BIS values were less than 20 or 40 for at least 5 minutes were 35 (1.9%) and 1701 (91.4%), respectively. The number of patients whose EEG suppression lasted for at least 5 minutes were 134 (7.2%).

90−day Mortality

A comparison between patients with a 90-day mortality and those without a 90-day mortality is presented in Table 2.

In univariable analysis, age, male gender, dysrhythmia, chronic obstructive pulmonary disease, pulmonary hypertension, malignancy, diabetes, ASA class, hemoglobin levels, albumin levels, map50_dur and bis40map50_dur were found to be potential risk factors for 90-day mortality. After the first step of multivariable analysis, only bis40map50_dur was statistically significant (P = 0.046) among BIS or MAP derived variables. In the final multivariable analysis, male gender, dysrhythmia, hemoglobin levels, albumin levels, and bis40map50_dur (OR = 1.260, P = 0.019) were associated with 90-day mortality (Table 3). Hosmer and Lemeshow goodness of fit test is not significant at 5% (P = 0.927).

180-day Mortality

A comparison between patients with a 180-day mortality and those without a 180-day mortality is presented in Table 4.

In univariable analysis, age, male gender, BMI, category of operation, dysrhythmia, pulmonary hypertension, malignancy, diabetes, ASA class, hemoglobin levels, albumin levels and bis40map50_dur were found to be potential risk factors for 180-day mortality. In multivariable analysis, category of surgical procedures, dysrhythmia, malignancy, ASA class, hemoglobin levels and albumin levels were found to significantly predict 180-day mortality. No BIS or MAP derived variables had any significant relationship with 180-day mortality (Table 5). Hosmer and Lemeshow goodness of fit test is not significant at

5% (P = 0.326).

Postoperative Delirium

A comparison between patients with delirium and those without delirium is presented in Table 6.

In univariable analysis, age, duration of anesthesia, hypertension, dysrhythmia, stroke, malignancy, diabetes mellitus, regular use of anticonvulsants, regular use of benzodiazepine, ASA class, hemoglobin levels, albumin levels, bis20_dur, bis20_5min, eegsup_dur, eegsup_5min, map50_dur, bis40map50_dur and bis20map50_dur were revealed as potential risk factors for postoperative delirium. After the first step of multivariable analysis, bis20_dur ($P < 0.000$) and eegsup_dur ($P < 0.000$) were statistically significant. In the final multivariable analysis, age, regular use of anticonvulsant, regular use of benzodiazepine, albumin levels, eegsup_dur (OR = 1.045, $P < 0.000$) and map50_dur (OR = 1.201, P = 0.001) were associated with postoperative delirium (Table 7). Hosmer and Lemeshow goodness of fit test is not significant at 5% (P = 0.787).

There were no significant differences of mean propofol dose (2.86 μg/mL vs. 3.09 μg/mL respectively, 95% CI −0.65 to 1.19, P = 0.61) and MAC of volatile anesthetics (0.99 vol % vs. 0.96 vol % respectively, 95% CI −0.14 to 0.08, P = 0.62) between patients with and without postoperative delirium.

Tables

Table 1. Characteristics of cohort. Continuous variables are presented with their mean ± standard deviation, and categorical variables are presented with their number (percentage).

Variables	
Age (year)	61.1 ± 12.9
Male gender	1088 (58.4%)
BMI (kg/m^2)	23.4 ± 3.5
Category of surgical procedures	
Stomach	492 (26.4%)
Colorectal	719 (38.6%)
Hepatic	154 (8.3%)
Biliary−pancreas	497 (26.%)
Type of anesthesia	
Total intravenous anesthesia	865 (46.5%)
Inhalation anesthesia	997 (53.5%)
Duration of anesthesia (min)	196.6 ± 104.4
BIS−derived variables	
bis40_dur (min)	70.5 ± 73.2
bis40_5min	1701 (91.4%)
bis20_dur (min)	0.5 ± 4.2
bis20_5min	35 (1.9%)
eegsup_dur (min)	1.6 ± 6.6
eegsup_5min	134 (7.2%)
bis40map50_dur (min)	0.34 ± 0.92
bis20map50_dur (min)	0.01 ± 0.11
map50_dur (min)	0.8 ± 1.7
Past medical history	
Aortic stenosis	10 (0.5%)
Congestive heart failure	6 (0.3%)

Coronary artery disease	98 (5.3%)
Hypertension	706 (37.9%)
Peripheral vascular occlusive disease	6 (0.3%)
Dysrhythmia	61 (3.3%)
Chronic obstructive pulmonary disease	46 (2.5%)
Pulmonary hypertension	7 (0.4%)
Stroke	70 (3.8%)
Malignancy	1368 (73.5%)
Diabetes	398 (21.4%)
Sleep apnea	3 (0.2%)
Medication history	
Anticonvulsant use	48 (2.6%)
Benzodiazepine use	67 (3.6%)
Opioid use	55 (3.0%)
Social history	
Current smoker	255 (13.7%)
Regular alcohol ingestion	449 (24.1%)
ASA class	
I	456 (24.5%)
II	1181 (63.4%)
III	221 (11.9%)
IV	4 (0.2%)
Laboratory tests	
Hemoglobin (g/dL)	10.5 ± 3.7
Albumin (g/dL)	3.7 ± 1.0

* BMI, body mass index; bis40_dur, cumulative time in which BIS values were less than 40; bis40_5min, incidence in which cumulative time of BIS values less than 40 lasted more than 5 minutes; bis20_dur, cumulative time in which BIS values were less than 20; bis20_5min, incidence in which cumulative time of BIS values less than 20 lasted more than 5 minutes; eegsup_dur, cumulative time in which patient' s EEG was suppressed; eegsup_5min, incidence in which cumulative time of EEG suppression lasted more than 5 minutes; bis40map50_dur, cumulative time that BIS values were less than 40 and MAP

was less than 50 mmHg simultaneously; bis20map50_dur, cumulative time that BIS values were less than 20 and MAP was less than 50 mmHg simultaneously; map50_dur, cumulative time that MAP was less than 50 mmHg; ASA class, the American Society of Anesthesiologists physical status

Table 2. Characteristics of the patients with or without 90-day mortality. Continuous variables are presented with their mean ± standard deviation or median [interquartile range], and categorical variables are presented with their number (percentage).

Variables	Died (n = 28)	Survived (n = 1834)	*P*-value
Age (year)	64.6 ± 12.9	61.0 ± 12.9	0.157
Male gender	22 (78.6%)	1066 (58.1%)	0.029
BMI (kg/m^2)	23.3 [4.3]	23.4 ± 3.5	0.305
Category of surgical procedures			0.214
Stomach	6 (21.4%)	486 (26.5%)	
Colorectal	16 (57.1%)	703 (38.3%)	
Hepatic	2 (7.1%)	152 (8.3%)	
Biliary-pancreas	4 (14.3%)	493 (26.9%)	
Type of anesthesia			0.998
Total intravenous anesthesia	13 (46.4%)	852 (46.5%)	
Inhalation anesthesia	15 (53.6%)	982 (53.5%)	
Duration of anesthesia (min)	181 [158]	196.7 ± 104.1	0.410
BIS-derived variables			
bis40_dur (min)	44.0 [89.8]	70.5 ± 72.8	0.599
bis40_5min	27 (96.4%)	1674 (91.2%)	0.507
bis20_dur (min)	0.0 [0.0]	0.5 ± 4.3	0.380
bis20_5min	0 (0%)	35 (1.9%)	1.000
eegsup_dur (min)	0.0 [0.4]	1.6 ± 6.6	0.006
eegsup_5min	1 (3.6%)	133 (7.2%)	0.717
bis40map50_dur (min)	0.00 [0.18]	0.33 ± 0.92	0.540
bis20map50_dur (min)	0.00 [0.00]	0.01 ± 0.11	0.013
map50_dur (min)	0.0 [1.0]	0.8 ± 1.7	0.324
Postoperative delirium	3 (10.7%)	27 (1.5%)	0.009
Past medical history			

Aortic stenosis	0 (0%)	10 (0.5%)	1.000
Congestive heart failure	0 (0%)	6 (0.3%)	1.000
Coronary artery disease	2 (7.1%)	96 (5.2%)	0.656
Hypertension	10 (35.7%)	696 (37.9%)	0.809
PVOD	0 (0%)	6 (0.3%)	1.000
Dysrhythmia	4 (14.3%)	57 (3.1%)	0.012
COPD	2 (7.1%)	44 (2.4%)	0.151
Pulmonary hypertension	1 (3.6%)	6 (0.3%)	0.101
Stroke	0 (0%)	70 (3.8%)	0.623
Malignancy	26 (92.9%)	1342 (73.2%)	0.017
Diabetes	10 (35.7%)	388 (21.2%)	0.062
Sleep apnea	0 (0%)	3 (0.2%)	1.000
Social history			
Current smoker	6 (21.4%)	249 (13.6%)	0.230
Regular alcohol ingestion	6 (21.4%)	443 (24.1%)	0.738
ASA class			0.002
I	1 (3.6%)	455 (24.8%)	
II	18 (64.3%)	1163 (63.4%)	
III	9 (32.1%)	212 (11.6%)	
IV	0 (0%)	4 (0.2%)	
Laboratory tests			
Hemoglobin (g/dL)	10.6 ± 2.0	12.7 ± 1.9	0.000
Albumin (g/dL)	2.9 ± 0.6	3.8 ± 0.6	0.000

* BMI, body mass index; bis40_dur, cumulative time in which BIS values were less than 40; bis40_5min, incidence in which cumulative time of BIS values less than 40 lasted more than 5 minutes; bis20_dur, cumulative time in which BIS values were less than 20; bis20_5min, incidence in which cumulative time of BIS values less than 20 lasted more than 5 minutes; eegsup_dur, cumulative time in which patient’ s EEG was suppressed; eegsup_5min, incidence in which cumulative time of EEG suppression lasted more than 5 minutes; bis40map50_dur, cumulative time that BIS values were less than 40 and MAP was less than 50 mmHg simultaneously; bis20map50_dur, cumulative time that BIS values were less than 20 and MAP was less than 50 mmHg

simultaneously; map50_dur, cumulative time that MAP was less than 50 mmHg; PVOD, peripheral vascular occlusive disease; COPD, chronic obstructive pulmonary disease; ASA class, the American Society of Anesthesiologists physical status

Table 3. Multivariable predictors of 90-day postoperative mortality.

Factor	P-value	Odds ratio	95% CI	
Male gender	0.017	3.216	1.237	8.356
History of dysrhythmia	0.021	4.255	1.241	14.594
Hemoglobin level (g/dL)	0.004	0.699	0.548	0.892
Albumin level (g/dL)	0.000	0.205	0.090	0.465
bis40map50_dur (min)	0.019	1.260	1.038	1.530

* bis40map50_dur, cumulative time that BIS values were less than 40 and MAP was less than 50 mmHg simultaneously

Table 4. Characteristics of the patients with or without 180-day mortality. Continuous variables are presented with their mean ± standard deviation or median [interquartile range], and categorical variables are presented with their number (percentage).

Variables	Died (n = 59)	Survived (n = 1803)	*P*-value
Age (year)	65.5 ± 11.7	60.9 ± 12.9	0.007
Male gender	40 (67.8%)	1048 (58.1%)	0.138
BMI (kg/m^2)	21.8 ± 4.4	23.4 ± 3.5	0.001
Category of surgical procedures			0.005
Stomach	9 (15.3%)	483 (26.8%)	
Colorectal	35 (59.3%)	684 (37.9%)	
Hepatic	6 (10.2%)	148 (8.2%)	
Biliary-pancreas	9 (15.3%)	488 (27.1%)	
Type of anesthesia			0.492
Total intravenous anesthesia	30 (50.8%)	835 (46.3%)	
Inhalation anesthesia	29 (49.2%)	968 (53.7%)	
Duration of anesthesia (min)	178 [158]	196.7 ± 104.1	0.498
BIS-derived variables			
bis40_dur (min)	43.7 [88.6]	70.5 ± 72.9	0.867
bis40_5min	55 (93.2%)	1646 (91.3%)	0.814
bis20_dur (min)	0.0 [0.0]	0.5 ± 4.3	0.806
bis20_5min	2 (3.4%)	33 (1.8%)	0.305
eegsup_dur (min)	0.0 [0.4]	1.6 ± 6.6	0.000
eegsup_5min	5 (8.5%)	129 (7.2%)	0.699
bis40map50_dur (min)	0.00 [0.18]	0.92 ± 0.11	0.894
bis20map50_dur (min)	0.00 [0.00]	0.34 ± 0.01	0.021
map50_dur (min)	0.0 [1.0]	0.8 ± 1.7	0.913
Postoperative delirium	3 (5.1%)	27 (1.5%)	0.067
Past medical history			

Aortic stenosis	1 (1.7%)	9 (0.5%)	0.276
Congestive heart failure	0 (0%)	6 (0.3%)	1.000
Coronary artery disease	2 (3.4%)	96 (5.3%)	0.767
Hypertension	25 (42.4%)	681 (37.8%)	0.473
PVOD	0 (0%)	6 (0.3%)	1.000
Dysrhythmia	7 (11.9%)	54 (3.0%)	0.000
COPD	2 (3.4%)	44 (2.4%)	0.655
Pulmonary hypertension	1 (1.7%)	6 (0.3%)	0.202
Stroke	1 (1.7%)	69 (3.8%)	0.724
Malignancy	55 (93.2%)	1313 (72.8%)	0.000
Diabetes	21 (35.6%)	377 (20.9%)	0.007
Sleep apnea	0 (0%)	3 (0.2%)	1.000
Social history			
Current smoker	9 (15.3%)	246 (13.6%)	0.723
Regular alcohol ingestion	11 (18.6%)	438 (24.3%)	0.318
ASA class			0.000
I	2 (3.4%)	454 (25.2%)	
II	38 (64.4%)	1143 (63.4%)	
III	19 (32.2%)	202 (11.2%)	
IV	0 (0%)	4 (0.2%)	
Laboratory tests			
Hemoglobin (g/dL)	10.7 ± 1.8	12.7 ± 1.8	0.000
Albumin (g/dL)	3.0 ± 0.6	3.8 ± 0.6	0.000

* BMI, body mass index; bis40_dur, cumulative time in which BIS values were less than 40; bis40_5min, incidence in which cumulative time of BIS values less than 40 lasted more than 5 minutes; bis20_dur, cumulative time in which BIS values were less than 20; bis20_5min, incidence in which cumulative time of BIS values less than 20 lasted more than 5 minutes; eegsup_dur, cumulative time in which patient' s EEG was suppressed; eegsup_5min, incidence in which cumulative time of EEG suppression lasted more than 5 minutes; bis40map50_dur, cumulative time that BIS values were less than 40 and MAP was less than 50 mmHg simultaneously; bis20map50_dur, cumulative time that BIS values were less than 20 and MAP was less than 50 mmHg

simultaneously; map50_dur, cumulative time that MAP was less than 50 mmHg; PVOD, peripheral vascular occlusive disease; COPD, chronic obstructive pulmonary disease; ASA class, the American Society of Anesthesiologists physical status

Table 5. Multivariable predictors of 180-day postoperative mortality.

Factor	*P*-value	Odds ratio	95% CI	
Category of procedures (compared with stomach surgery)	0.008			
Biliary-Pancreas	0.678	1.232	0.460	3.301
Hepatic	0.260	1.890	0.625	5.716
Colorectal	0.003	3.336	1.507	7.386
History of dysrhythmia	0.012	3.430	1.307	9.004
History of malignancy	0.040	3.082	1.051	9.033
Higher ASA class (compared with class I)	0.055			
ASA class II	0.122	3.171	0.734	13.696
ASA class III	0.018	6.207	1.361	28.307
ASA class IV	0.999	0.000	0.000	
Hemoglobin level (g/dL)	0.014	0.791	0.656	0.954
Albumin level (g/dL)	0.000	0.175	0.097	0.315

* ASA class, the American Society of Anesthesiologists physical status

Table 6. Characteristics of the patients with or without postoperative delirium. Continuous variables are presented with their mean ± standard deviation or median [interquartile range], and categorical variables are presented with their number and (percentage).

Variables	Delirium (n = 30)	No delirium (n = 1832)	*P*-value
Age (year)	70.7 ± 12.1	60.9 ± 12.8	0.000
Male gender	19 (63.3%)	1069 (58.4%)	0.583
BMI (kg/m^2)	23.8 ± 5.1	23.4 ± 3.5	0.641
Category of surgical procedures			0.227
Stomach	7 (23.3%)	485 (26.5%)	
Colorectal	8 (26.7%)	711 (38.8%)	
Hepatic	5 (16.7%)	149 (8.1%)	
Biliary-pancreas	10 (33.3%)	487 (26.6%)	
Type of anesthesia			0.981
Total intravenous anesthesia	14 (46.7%)	851 (46.5%)	
Inhalation anesthesia	16 (53.3%)	981 (53.5%)	
Duration of anesthesia (min)	275.4 ± 140.4	195.3 ± 103.3	0.004
BIS-derived variables			
bis40_dur (min)	43.4 [88.7]	70.2 ± 73.1	0.233
bis40_5min	28 (93.3%)	1673 (91.3%)	1.000
bis20_dur (min)	0.0 [0.0]	0.4 ± 3.4	0.008
bis20_5min	5 (16.7%)	30 (1.6%)	0.000
eegsup_dur (min)	0.02 [0.41]	1.4 ± 5.6	0.000
eegsup_5min	7 (23.3%)	127 (6.9%)	0.001
bis40map50_dur (min)	0.00 [0.18]	0.34 ± 0.92	0.115
bis20map50_dur (min)	0.00 [0.00]	0.01 ± 0.11	0.019
map50_dur (min)	0.0 [1.0]	0.8 ± 1.7	0.000
Postoperative outcomes			
90-day mortality	3 (10.0%)	25 (1.4%)	0.009

180−day mortality	3 (10.0%)	56 (3.1%)	0.067
Past medical history			
Aortic stenosis	0 (0%)	10 (0.5%)	1.000
Congestive heart failure	0 (0%)	6 (0.3%)	1.000
Coronary artery disease	2 (6.7%)	96 (5.2%)	0.670
Hypertension	18 (60.0%)	688 (37.6%)	0.012
PVOD	0 (0%)	6 (0.3%)	1.000
Dysrhythmia	4 (13.3%)	57 (3.1%)	0.015
COPD	1 (3.3%)	45 (2.5%)	0.531
Pulmonary hypertension	0 (0%)	7 (0.4%)	1.000
Stroke	4 (13.3%)	66 (3.6%)	0.024
Malignancy	26 (86.7%)	1342 (73.3%)	0.142
Diabetes	12 (40.0%)	386 (21.1%)	0.012
Sleep apnea	0 (0%)	3 (0.2%)	1.000
Medication history			
Anticonvulsant use	4 (13.3%)	44 (2.4%)	0.007
Benzodiazepine use	8 (26.7%)	59 (3.2%)	0.000
Opioid use	1 (3.3%)	54 (2.9%)	0.596
Social history			
Current smoker	5 (16.7%)	250 (13.6%)	0.633
Regular alcohol ingestion	5 (16.7%)	444 (24.2)%	0.336
ASA class			0.000
I	1 (3.3%)	455 (24.8%)	
II	21 (70.0%)	1160 (63.3%)	
III	7 (23.3%)	214 (11.7%)	
IV	1 (3.3%)	3 (0.2%)	
Laboratory tests			
Hemoglobin (g/dL)	12.2 ± 2.1	12.7 ± 1.9	0.145
Albumin (g/dL)	2.5 [1.0]	3.8 ± 0.6	0.000

* BMI, body mass index; bis40_dur, cumulative time in which BIS values were less than 40; bis40_5min, incidence in which cumulative time of BIS values less than 40 lasted more than 5 minutes; bis20_dur, cumulative time in which BIS values were less than 20; bis20_5min, incidence in which cumulative time of

BIS values less than 20 lasted more than 5 minutes; eegsup_dur, cumulative time in which patient's EEG was suppressed; eegsup_5min, incidence in which cumulative time of EEG suppression lasted more than 5 minutes; bis40map50_dur, cumulative time that BIS values were less than 40 and MAP was less than 50 mmHg simultaneously; bis20map50_dur, cumulative time that BIS values were less than 20 and MAP was less than 50 mmHg simultaneously; map50_dur, cumulative time that MAP was less than 50 mmHg; PVOD, peripheral vascular occlusive disease; COPD, chronic obstructive pulmonary disease; ASA class, the American Society of Anesthesiologists physical status

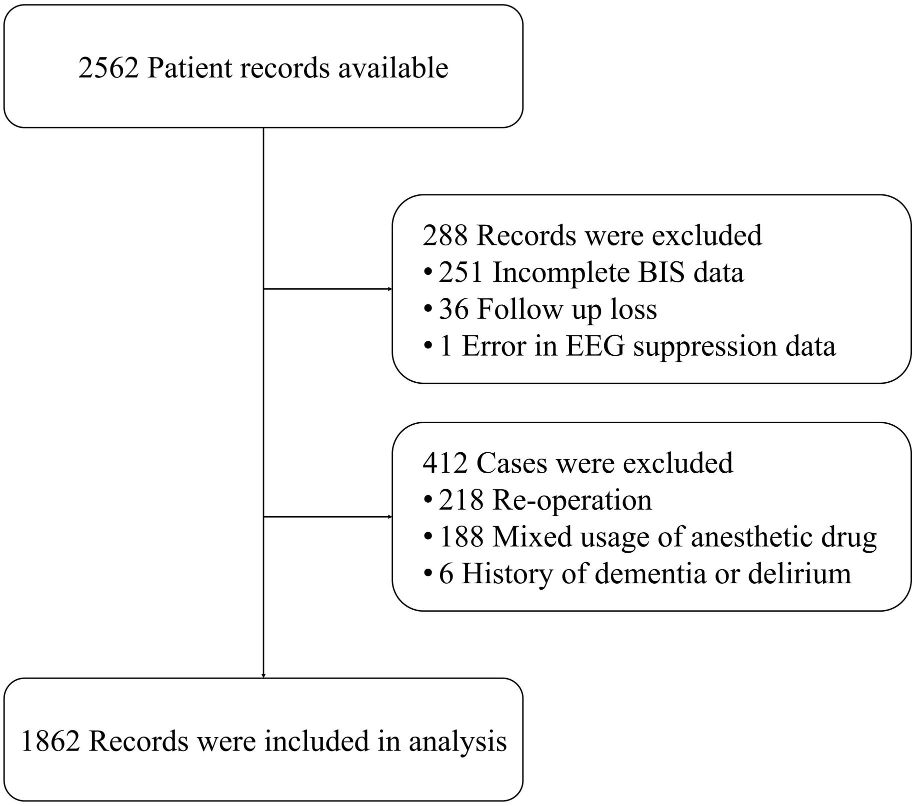
Table 7. Multivariable predictors of postoperative delirium.

Factor	*P*-value	Odds ratio	95% CI	
Age (year)	0.027	1.044	1.005	1.084
Anticonvulsant use	0.025	3.991	1.193	13.349
Benzodiazepine use	0.000	6.980	2.603	18.717
Albumin level (g/dL)	0.001	0.316	0.161	0.620
eegsup_dur (min)	0.000	1.045	1.024	1.067
map50_dur (min)	0.001	1.201	1.083	1.333

* eegsup_dur, cumulative time in which patient's EEG was suppressed; map50_dur, cumulative time that MAP was less than 50 mmHg

Figures

Figure 1. CONSORT diagram.



DISCUSSION

The major findings of this study were that the duration of BIS values below 40 coupled with MAP less than 50 mmHg was associated with 90-day postoperative mortality and that the duration of EEG suppression and the duration of MAP less than 50 mmHg were both associated with postoperative delirium. This suggests that excessive anesthetic-induced brain suppression as well as intraoperative hypotension may be associated with adverse postoperative outcome.

The Vital Recorder program, which was used to collect BIS values, suppression ratios and MAP data in this study, is an automatic recording device for obtaining high-resolution time-synchronized physiological data from multiple anesthesia devices. With this software we could obtain stored digitalized data for every patient, as well as accurately compute the independent variables related to BIS and MAP. Furthermore, intraoperative target site propofol concentrations in total intravenous anesthesia and MAC of volatile agents in inhalational anesthesia were recorded in real time.

This study found that the 'simultaneous double low', the cumulative time of BIS values less than 40 coupled with MAP less than 50 mmHg was associated with 90-day postoperative mortality. In contrast, the cumulative durations of BIS values less than 40, BIS values less than 20, and EEG suppression alone were not related to postoperative mortality, similar to several previous reports (7, 11). The simultaneous double low of BIS values less than 20 and MAP less than 50 mmHg was not related to postoperative mortality even in univariable analysis, however. This is probably due to the duration of the total 'double low' time being too short.

The simultaneous double low of BIS values less than 40 and MAP less than 50 mmHg was not associated with postoperative 180-day mortality. This finding suggests that intraoperative low BIS values and blood pressure seem to be related to early-to-intermediate postoperative mortality and not to intermediate-to-long term mortality. Additional risk factors in our multivariable regression model in 180-day mortality compared to 90-day mortality were category of surgical procedures, history of malignancy and ASA class, implying that the impact of intraoperative anesthesia-related profiles is smaller compared to patient's own clinical risk factors.

Common risk factors in 90-day and 180-day mortality in this study were history of dysrhythmia, preoperative low hemoglobin levels, and preoperative low albumin levels. Preoperative dysrhythmia, especially atrial fibrillation, was shown to be a risk factor of postoperative mortality following cardio-thoracic surgery (21, 22). Preoperative anemia was associated with increased postoperative mortality in both cardiac and non-cardiac surgery patients (23, 24). Additionally, preoperative hypo-albuminemia is known as a predictor of postoperative mortality following urological surgeries (25, 26). Also, male gender was significantly associated with 90-day postoperative mortality and several retrospective studies revealed a similar tendency in patients within 30-days of undergone major surgery (27, 28).

Willingham and colleagues used the concept 'interaction term' in their study (11), which compared patients in the EEG suppressed group who had low MAP with their non-suppressed counterparts without low arterial pressure. Daniel and colleagues used the concept 'double low' (9), meaning that the patient's intraoperative mean BIS and MAP values were both lower than population mean values. The concept of a 'simultaneous double low', which we used in this study, is relatively novel. There are as of today no studies which have sought to look the combined effect of low BIS values and low MAP maintained for a specific period of time.

In multivariable prediction models of postoperative delirium, patient's age, preoperative albumin levels and regular use of benzodiazepine were significant predictors of postoperative delirium, consistent with previous study results (29-31). Some previous studies suggested that anticonvulsants were helpful in preventing postoperative delirium in older patients who underwent spine surgery (32) and that they was able to reduce the severity of delirium in patients following cardiac surgery (33). However, unlike the use of anticonvulsants for prophylactic purposes in delirium, other studies revealed that preoperative exposure to anticonvulsants caused postoperative delirium (34, 35), consistent with the results of this study.

Besides EEG suppression, the cumulative duration of MAP less than 50 mmHg was an independent risk factor for postoperative delirium in our study. This result contradicts previous studies that could not find an association between intraoperative hypotension and postoperative delirium in both non-cardiac (19) and cardiac surgery patients (36). Although the lower limit of cerebral autoregulation fluctuates widely (37), the cutoff of 50 mmHg is lowest among the values suggested. Therefore, an MAP of less than 50 mmHg could be out of the range of cerebral autoregulation and prolonged intraoperative hypotension could have temporary or persistent adverse effects on the brain. Delicate control of anesthetic depth and blood pressure would be crucial to protect the patient from postoperative delirium.

In this study, mean propofol and volatile anesthetic concentrations were not statistically different between patients with or without postoperative delirium. Therefore, patients who presented postoperative delirium may have had higher anesthetic vulnerability, because BIS values less than 20 and EEG suppression were observed more frequently in these patients at similar anesthetic concentration. BIS monitoring and titration of anesthetics can help avoid unnecessarily deep anesthesia and possible neurotoxic effects in vulnerable patients (38).

This study had several limitations. First, the incidence of postoperative mortality and delirium was relatively smaller than that in previous reports (39, 40). For a more accurate statistical analysis, a larger number of cases would be needed. It is possible that retrospective investigation of postoperative delirium based on data from electronic medical records could under-estimate the incidence of postoperative delirium. Moreover, the data were restricted to major abdominal surgeries, and intermediate-to-long term postoperative outcomes were largely related to other covariates such as type of surgery and history of malignancy. The incidence of malignancy was especially high in the cohort of this study, but we did not assess and reflect the causes of death or stage of cancer. To evaluate the sole effect of anesthesia, a larger number of cases with diverse types of diseases and operations would be needed.

Finally, it was difficult to collect all relevant clinical data such as preoperative cognitive function, due to retrospective design of this study. Nevertheless, all intraoperative data were completely obtained using the ‘Vital Recorder program.

In conclusion, the cumulative duration of BIS values less than 40 coupled with MAP less than 50 mmHg was associated with 90-day postoperative mortality. Meanwhile, the cumulative duration of EEG suppression as well as the cumulative duration of MAP less than 50 mmHg were associated with postoperative delirium. Delicate intraoperative management of anesthesia depth and blood pressure is important to avoid excessive brain suppression and hypotension, which could be associated with postoperative mortality and delirium.

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초록

수술 중 낮은 이중분광계수 값이 수술 후 사망률과 섬망 발생에 미치는 영향

배경: 수술 중 낮은 이중분광계수 값과 임상적 예후 사이의 관계는 논쟁의 여지가 있다. 이 연구는 복부 수술을 받는 환자에서 수술 중 낮은 이중분광계수 값이 수술 후 사망률 및 섬망 발생에 미치는 영향을 알아보고자 하였다.

방법: 이 연구는 후향적 연구이며 전신 마취를 받은 1862명의 환자를 대상으로 하였다. 이중분광계수 값이 20, 40보다 각각 낮았던 총 시간과 뇌파의 억제가 일어난 총 시간, 그리고 각 상태가 5분 이상 유지된 경우의 수를 조사하였다. 수술 중 평균 동맥압이 50 mmHg 미만으로 유지된 시간도 조사하였다. 수술 후 사망률과 섬망 발생에 대한 위험 인자를 밝히기 위해 다변량 로지스틱 회귀분석을 시행하였다.

결과: 90일 사망률, 180일 사망률, 섬망 발생률은 각각 1.5%, 3.2%, 그리고 1.6%였다. 이중분광계수 값이 40 미만이면서 동시에 평균 동맥압이 50 mmHg 미만이었던 총 시간이 90일 사망률과 통계적 연관성이 있었다 [odds ratio (OR) = 1.260, P = 0.019]. 이중분광계수 장치를 통해 획득한 변수들과 180일 사망률은 관련이 없었다. 뇌파가 억제되었던 총 시간과 수술 중 평균 동맥압이 50 mmHg 미만으로 유지된 총 시간이 각각 수술 후 섬망 발생과 유의한 연관성이 있었다 (OR = 1.045, P < 0.000; OR = 1.201, P = 0.001).

결론: 과도한 뇌 억제와 저혈압이 수술 후 사망률 및 섬망 발생과 관련이 있으며, 이에 수술 중 마취 심도와 혈압에 대한 섬세한 관리가 필요

하다.

주요어: 이중분광계수, 수술 중 저혈압, 수술 후 사망률, 섬망
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